APPROACHES TO THE BIOMIMETIC SYNTHESIS OF β-LACTAM ANTIBIOTICS

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submitted in partial fulfilment
of the requirements for the Degree
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by

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CONTENTS

ABSTRACT

The C4 benzoyloxy substituted β-lactams (65)-(68) were formed by the copper-promoted reaction of β-lactams (42)-(45) with *t*-butyl perbenzoate. The benzoyloxylation of the azetidin-2-one ring occurs at C4 with no competing reaction at the C3 position.

The relative ease of abstraction by *t*-butoxy radicals of hydrogens bonded to the endocyclic and exocyclic carbons adjacent to the amide nitrogen was determined from the reaction of the β-lactam (47). This reaction gave the endocyclic substituted β-lactam (69), the exocyclic substituted β-lactam (70) and the disubstituted β-lactam (71).

Substitution solely at the exocyclic carbon occured in the reaction of the β-lactam (48), which gave the β-lactam (73). The mode of substitution of the β-lactams (42)-(45), (47) and (48) is discussed.

Reaction of the γ-lactam (80) with *t*-butyl perbenzoate gave the C5 substituted γ-lactam (90) and the exocyclic substituted γ-lactam (87). The mode of formation and ratio of these two products is discussed.

Bromination of N-benzoylvaline methyl ester (19) with N-bromosuccinimide, followed by reaction with tri-*n*-butyltin hydride gave N-benzoyl-3-bromovaline methyl ester (93). The synthesis of this compound is discussed.

Reaction of 1-(1-methoxycarbonyl-2-methypropyl)azetidin-2-one (31) with sulphuryl chloride gave the azetidin-2-one (102). An independent synthesis of 1-(3-chloro-1-methoxycabonyl-2-methylpropyl)-3,3-dimethylazetidin-2-one (102) from N-(3-bromo-2,2-dimethylpropanoyl)valine methyl ester (100) is described and the mechanism of these reactions is discussed.

PUBLICATION

Part of the work described in this thesis has been published.

Easton, C.J., and Love, S.G., "Direct Introduction of a Benzoyloxy Substitution at the C4 Position of β-lactams", *Tetrahedron Letters*, 1986, 27, 2315.

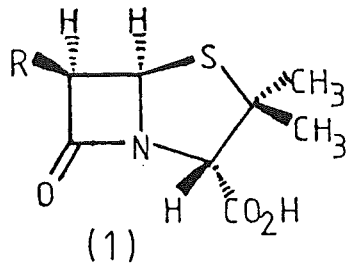
LIST OF SCHEMES

CHAPTER 1.

INTRODUCTION

Much of the credit for the discovery of the antibiotic penicillin goes to Fleming who in 1928 observed the antibacterial properties of the fungus *Penicillium notatum*.[1] He gave the name penicillin to the antibacterial substance produced by this fungal strain. Penicillin was first isolated by Chain, Florey and co-workers.[2] By 1946 the structure of penicillin was known,[3] but the first *in-vitro* synthesis was not achieved until 1957.[4]

The β-lactam ring plays a crucial role in the antibiotic activity of penicillin and a large number of antibiotics with this structural feature are known today. These include the penicillins (1) and cephalosporins (2), as well as the cephamycins (3), 1-oxacephems (4), clavulanic acid (5), penems (6), carbapenems (7), norcardicins (8) and monobactams (9). Many of the β-lactam antibiotics known today are synthetic or semi-synthetic.[5]



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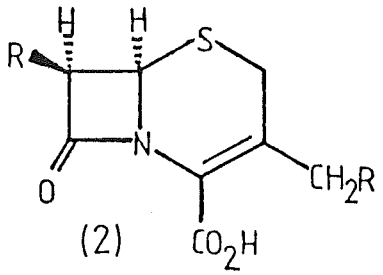

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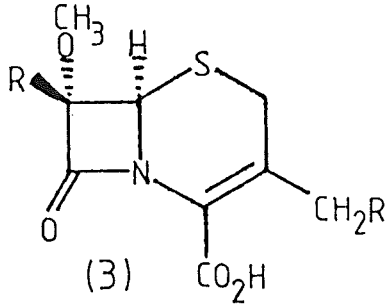

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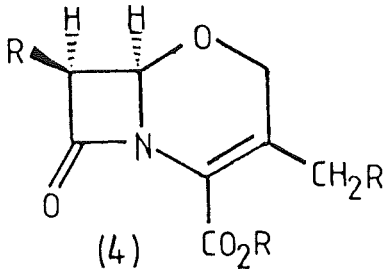

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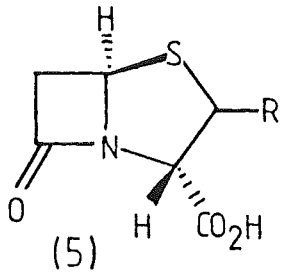

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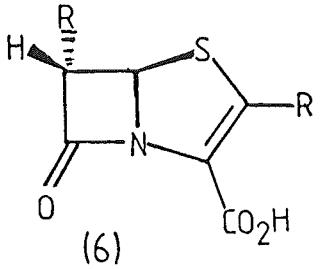

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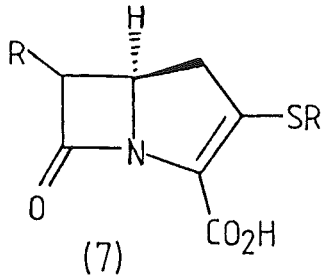

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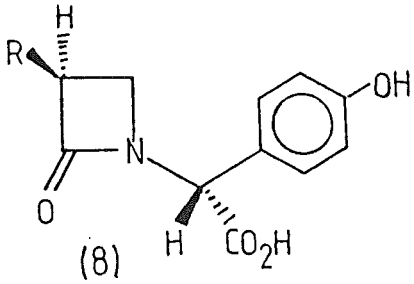

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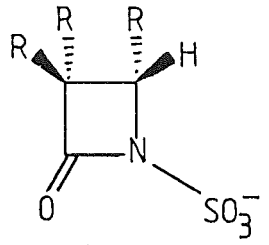
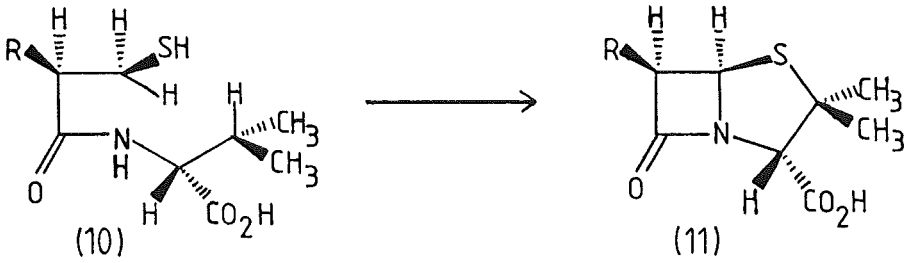


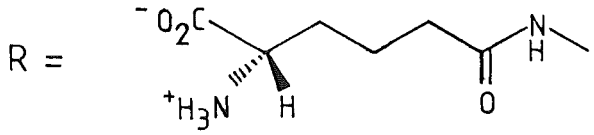
(9)

Investigations of the mechanism of biosynthesis of penicillins began in the early 1940's[3] and continue today. In 1960 Arnstein[6] identified the tripeptide [δ(L-α-aminoadipoyl)]-L-cysteinyl-D-valine*(LLD-ACV),(10) although the stereochemistry was not defined until 1971.[7] The tripeptide is accepted generally as the biosynthetic precursor to isopenicillin-N (11).[8] Isopenicillin-N is the precursor of the naturally occurring penicillins and cephalosporins.

* δ-α-aminoadipoyl = 5-amino-5-carboxypentanoyl

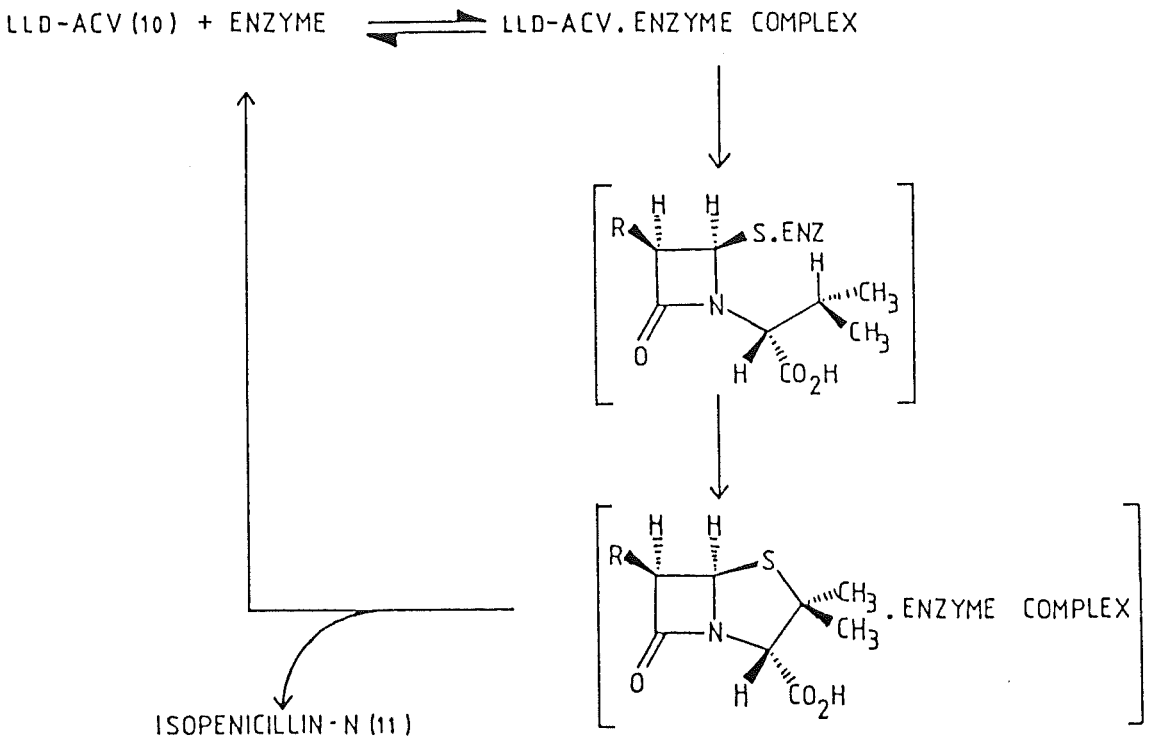


(10) (11)



The mechanism of biosynthesis of isopenicillin-N (11) from the tripeptide (10) has not been established with certainty. No intermediates between the tripeptide (10) and isopenicillin-N (11) have been isolated.[9,10] The only report of the detection of an intermediate[11] could not be confirmed.[10]

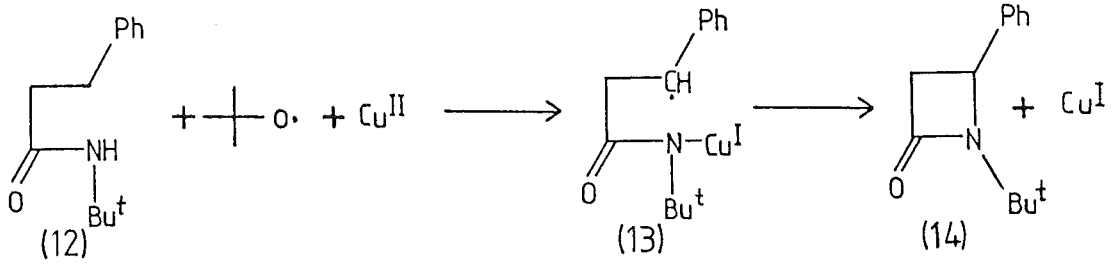
Baldwin and co-workers[12] recently reported the results of kinetic studies which show that the β-lactam ring forms before the thiazolidine ring (Scheme 1).



Scheme 1

Two mechanisms have been proposed to account for the formation of the β-lactam ring. One involves a free radical mechanism[13] and the other an ionic mechanism.[14] To date both mechanisms are consistent with the results of all biosynthetic studies.

A reaction to give β-lactams by oxidative free radical cyclisation was first demonstrated by Baldwin and Davis.[13] They reported that the acyclic amide (12) cyclised to give β-lactam (14), on reaction with di-*t* -butylperoxide in the presence of a copper salt catalyst (Scheme 2).

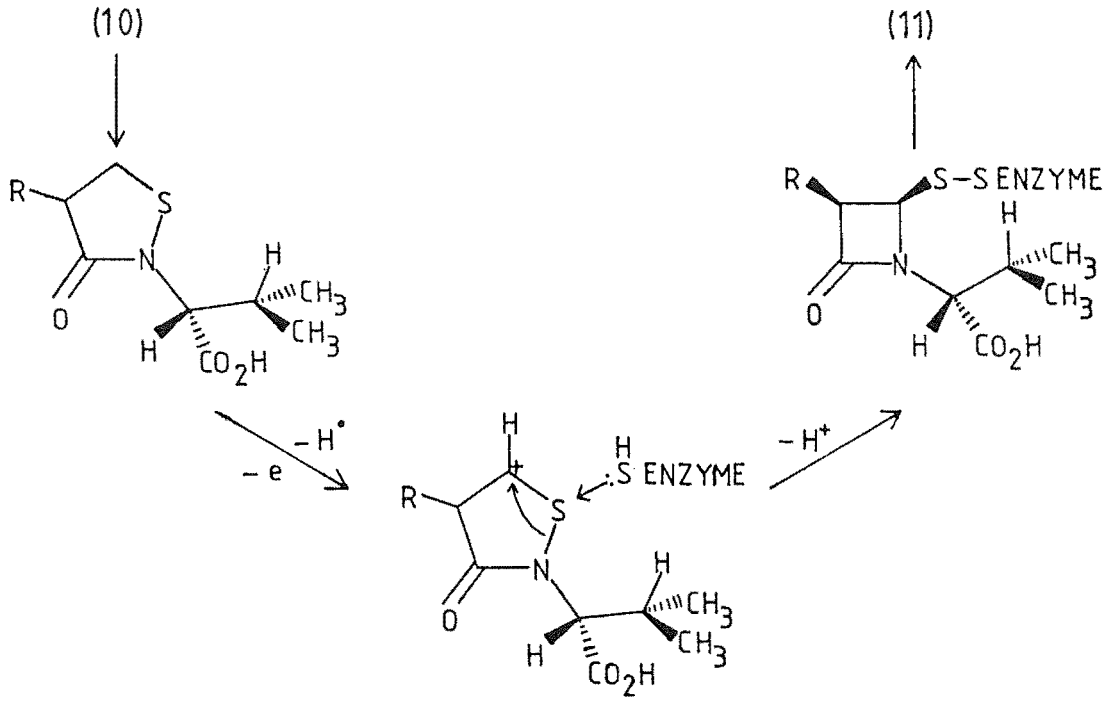


Scheme 2

Because of the dependence of the penicillin synthetase enzyme on Fe^{2+} and oxygen, they suggested that an organo-metal complex analogous to (13) might be involved in the *in-vivo* process of β-lactam ring formation.[15]

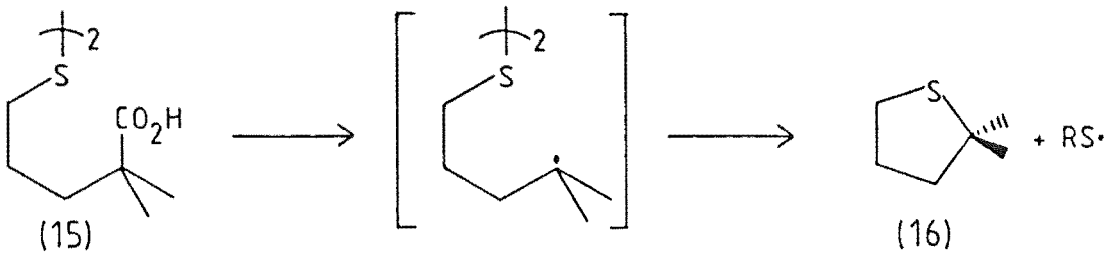
Beckwith and Easton[16] observed complimentary results in related systems. Recently Procter and co-workers[17] also observed radical cyclisation to give β-lactams.

Isothiazolidinones have been proposed as intermediates in the formation of the β-lactam ring in penicillin biosynthesis.[18] However, reactions with model compounds have shown that such a conversion is unlikely to involve radical intermediates.[18] Easton[14] has shown that ring contraction of isothiazolidinones to β-lactams does occur by an ionic mechanism. The mechanism he proposed for the *in-vivo* process (Scheme 3), also accounts for the role of the thiol group in binding the substrate to the enzyme[19] during the biosynthesis of penicillin.



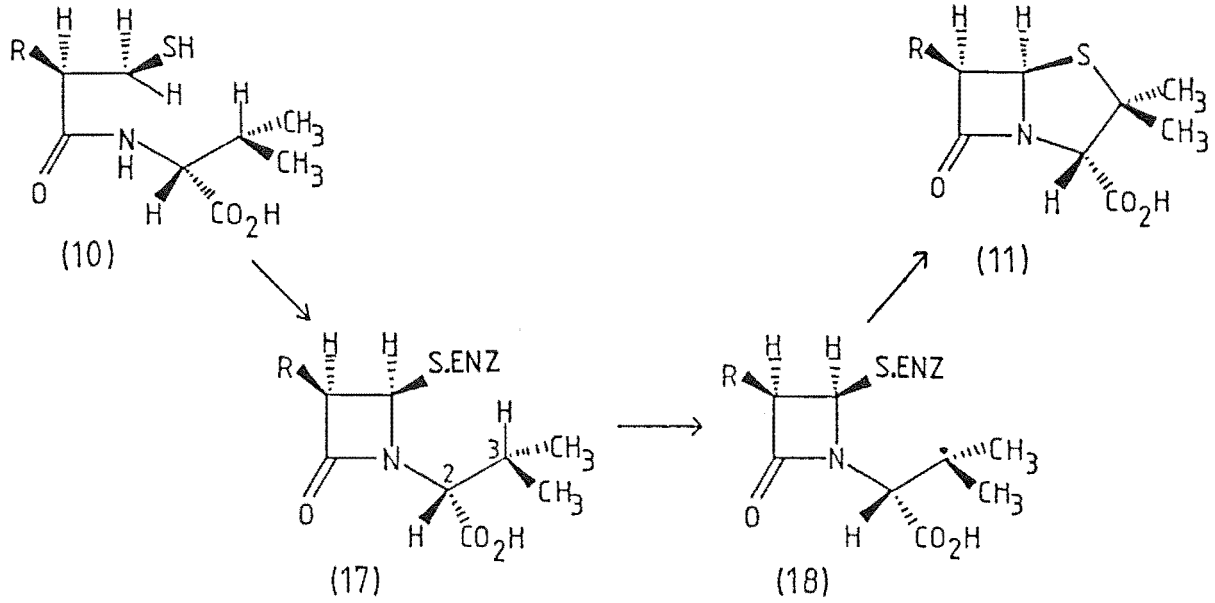
Scheme 3

Baldwin and Wan[20] first proposed a free-radical mechanism to account for the formation of the thiazolidine ring in penicillin biosynthesis. They reported that the model compound (15) cyclised to give (16) by a free-radical reaction pathway (Scheme 4).



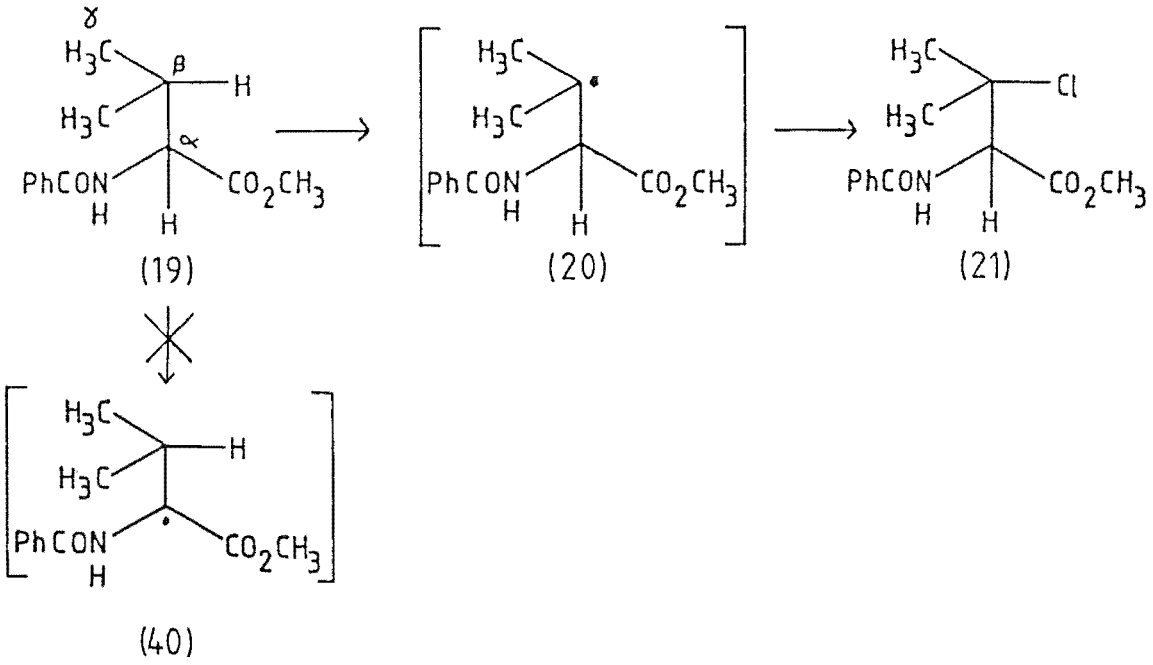
Scheme 4

On that basis they proposed the free-radical mechanism of formation of the thiazolidine ring shown in Scheme 5.



Scheme 5

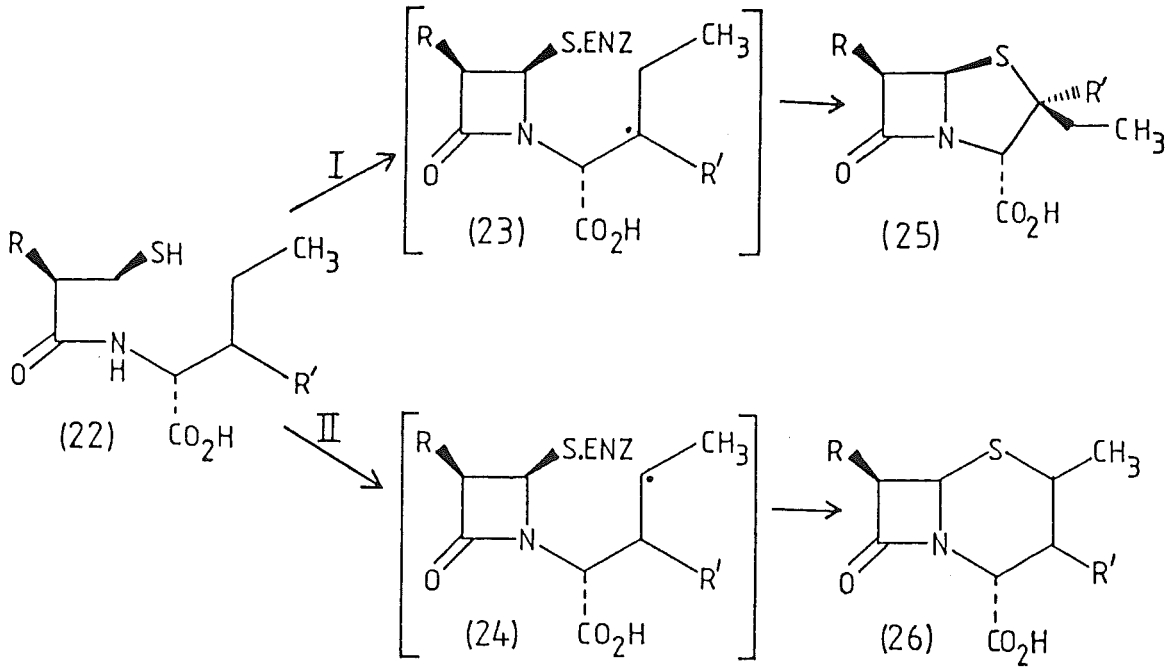
Easton and Bowman[21] established the chemical validity of the hydrogen atom transfer in the conversion of (17) into (18). Free-radical chlorination of the model compound (19) gave the β-chloro compound (21), and this result was attributed to reaction *via* the free radical intermediate (20) (Scheme 6). The hydrogen atom transfer in the conversion of (19) into (20) is analogous to the conversion of (17) into (18) in the biosynthesis of penicillin.



Scheme 6

Reaction of (19) occurs preferentially at the β-position despite the fact that the α-centred radical (40) would be expected to be more stable than (20). The α-radical (40) is stabilized by the combined resonance effects of an electron-donating amido substituent and an electron-withdrawing carboxy substituent.

Baldwin and co-workers[22] have reported enzyme-catalysed reactions of modified substrates, which are consistent with reaction *via* free-radical intermediates. They reported that the isopenicillin-N synthetase enzyme catalyses reactions of (22a) and (22b) to give the respective penams (25a) and (25b) and the corresponding cephams (26a) and (26b) (Scheme 7). The observed balance between the two reaction pathways may be interpreted in terms of the types of intermediate radicals, either tertiary or secondary, formed in the respective reactions.



a; $R' = CH_3$

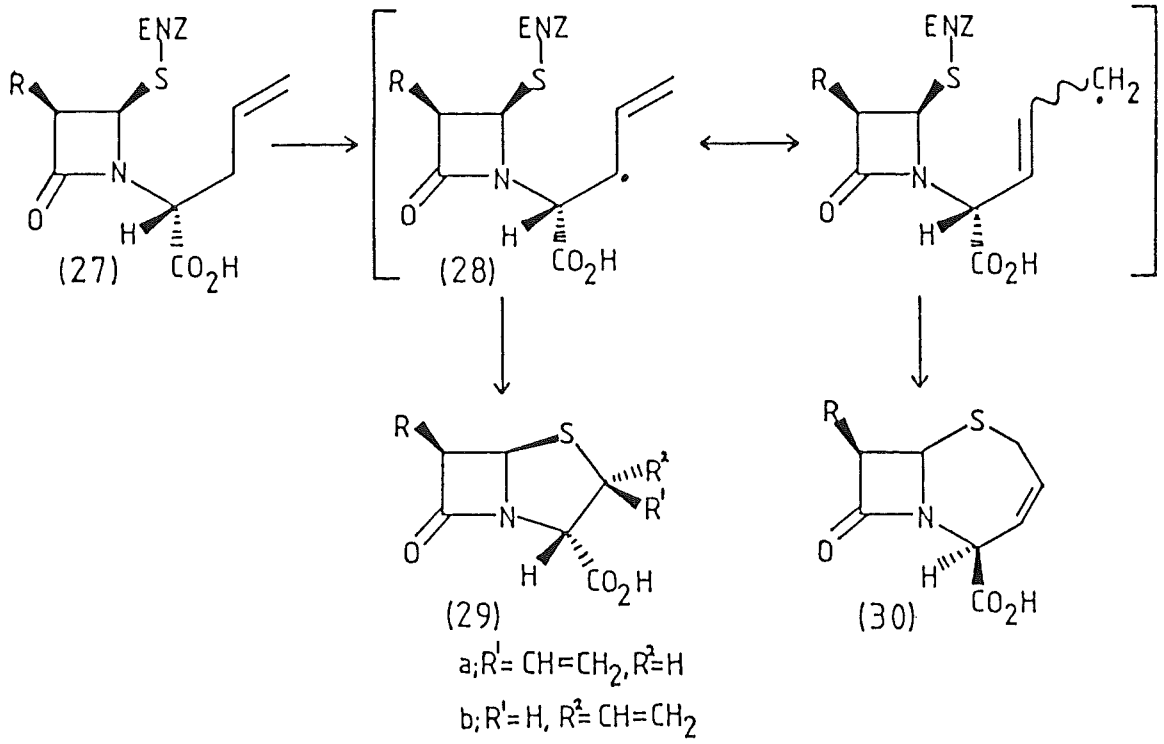
b; $R' = H$

Scheme 7

In the reaction of substrate (22a), pathway I predominates, because the tertiary radical (23a) forms in preference to the secondary radical (24a). For substrate (22b) both intermediate radicals, (23b) and (24b), are secondary radicals. In this case, pathway II predominates because the steric hinderance to reaction is less for this type of process.

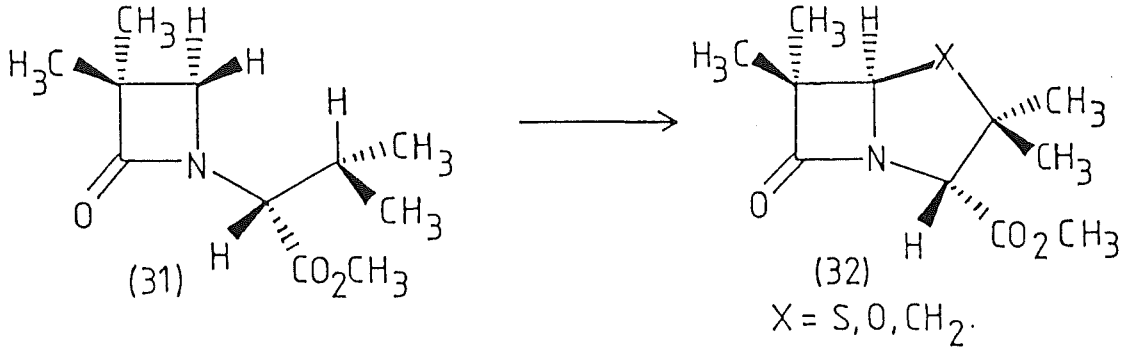
Further, Baldwin and co-workers[23] have shown that compound (27) undergoes enzyme-catalysed reaction to give a variety of products. The isolation of products (29a), (29b) and (30) is consistent with their formation *via* the intermediate allylic radical (28) (Scheme 8).

The aim of the work presented in this thesis was to develop a biomimetic synthesis of bicyclic β-lactam



Scheme 8

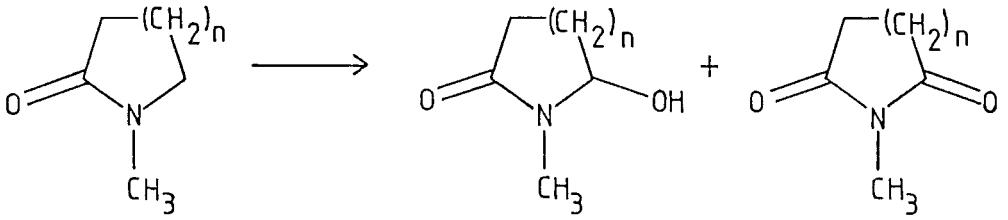
antibiotics from C4-unsubstituted azetidinones. As discussed above, it appears that the biosynthesis of the thiazolidine ring in isopenicillin-N (11) occurs by a free-radical mechanism, after β-lactam ring formation. The present proposal was to bring about ring formation as shown in Scheme 9, through free radical reactions of azetidinones such as (31).



Scheme 9

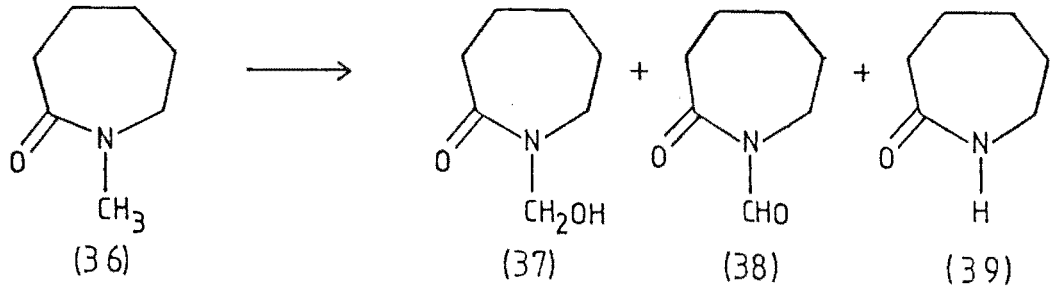
Prior to the conception of this project, direct functionalisation of azetidinones at C4 had not been reported. This apparent constraint has limited the use of azetidinones in the synthesis of bicyclic β-lactam antibiotics. A large number of azetidinones substituted at C4 are known, but none of these were obtained through direct functionalisation of an unsubstituted azetidinone.

Ban and co-workers[24] reported electrochemical oxidation of N-methyl substituted 5-, 6- and 7- membered ring lactams. Anodic oxidation of the lactams (33a) and (33b) gave the corresponding α-hydroxylated lactams (34a) and (34b) as the major products, with minor amounts of the respective imides (35a) and (35b) (Scheme 10).



Scheme 10

With the 7-membered ring lactam (36), oxidation occurred at the exocyclic carbon α to nitrogen to give the oxygenated compounds (37) and (38), and minor amounts of (39); the latter compound (39) was seen as the product of the loss of formaldehyde from (37) (Scheme 11).

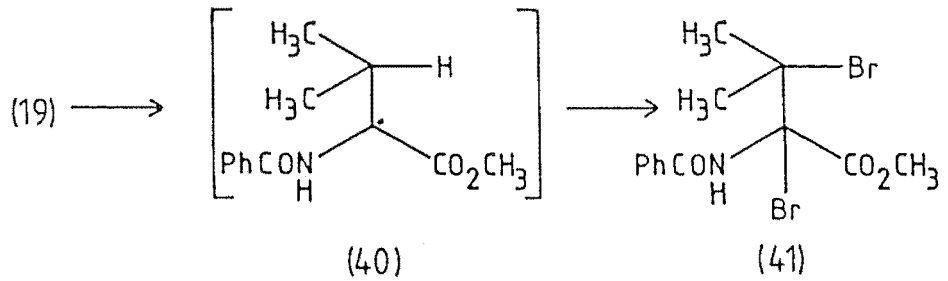


(36) (37) (38) (39)

Scheme 11

As free radical or oxidative processes result in functionalisation at the position adjacent to the amide nitrogen in these lactams, the possibility of using a similar process to functionalise β-lactams at C4 was investigated. This work is discussed in Chapter 2 of the thesis. Related work on the functionalisation of γ-lactams at C5 is discussed in Chapter 3 of the thesis.

In order to develop methods for the functionalisation of compound (31) at the β-valinyl position, reactions of the valine derivative (19) were investigated. The regioselective free-radical chlorination of (19) at C3 has been reported (Scheme 6).[21,25] Reaction of the valine derivative (19) with N-bromosuccinimide gave the dibromide (41), *via* initial reaction at C2 (Scheme 12).



(40) (41)

Scheme 12

This reversal of selectivity has been discussed in

terms of the relative degrees of C-H bond homolysis in the transition states of these reactions. There is little bond homolysis in the transition state of the chlorination reaction. The regioselectivity is controlled by the inductively electron - withdrawing effect of the amido and carboxy groups acting to retard attack at the α-position by electrophilic radicals involved in the hydrogen-atom abstraction. Bond homolysis is more advanced in the transition state of the bromination reaction. Hydrogen-atom transfer from the α-position is favoured, therefore, because the product radical (40) is stabilised by the resonance electron-donating amido and electron-withdrawing carboxy groups.

In Chapter 4 of this thesis work on the functionalisation of the valine derivative (19) is discussed. In this connection a particular aim was the regioselective incorporation of bromine at the C3 position, because of the anticipated greater ease of displacement of bromine, compared with chlorine, in subsequent reactions.

In Chapter 5 of this thesis attempts to apply the information described in Chapters 2, 3 and 4 of the thesis to the synthesis of bicyclic β-lactams are discussed.

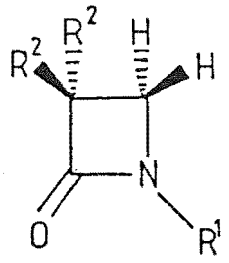
CHAPTER 2

Results and Discussion

Functionalisation of β-Lactams at the C4 Position

2.1 Preparation of the Azetidin-2-ones (42)-(48).

The azetidin-2-ones (42)-(48) were synthesised to investigate their possible functionalisation at the C4 position.



(42) $R^1 = Bu^t$, $R^2 = CH_3$

(43) $R^1 = Ph$, $R^2 = CH_3$

(44) $R^1 = Bu^t$, $R^2 = H$

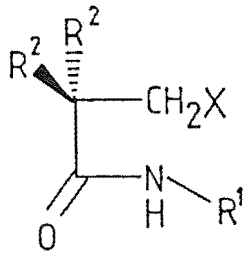
(45) $R^1 = Ph$, $R^2 = H$

(46) $R^1 = Bu^t$, $R^2 = Ph$

(47) $R^1 = CH_3$, $R^2 = CH_3$

(48) $R^1 = CH_2Ph$, $R^2 = CH_3$

In summary all seven azetidin-2-ones were prepared by similar methods involving preparation of the respective haloamides (49)-(55) and cyclisation of these haloamides to give the corresponding azetidin-2-ones (42)-(48).



(49) $R^1 = Bu^t$, $R^2 = CH_3$, X = Cl

(50) $R^1 = Ph$, $R^2 = CH_3$, X = Br

(51) $R^1 = Bu^t$, $R^2 = H$, X = I

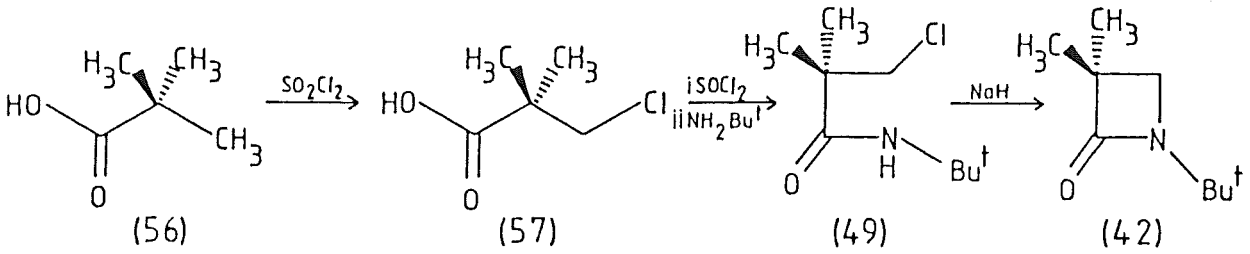
(52) $R^1 = Ph$, $R^2 = H$, X = Cl

(53) $R^1 = Bu^t$, $R^2 = Ph$, X = Cl

(54) $R^1 = CH_3$, $R^2 = CH_3$, X = Br

(55) $R^1 = CH_2Ph$, $R^2 = CH_3$, X = Br

The azetidin-2-one (42) was synthesised from dimethyl-propanoic acid (56), as shown in Scheme 13.



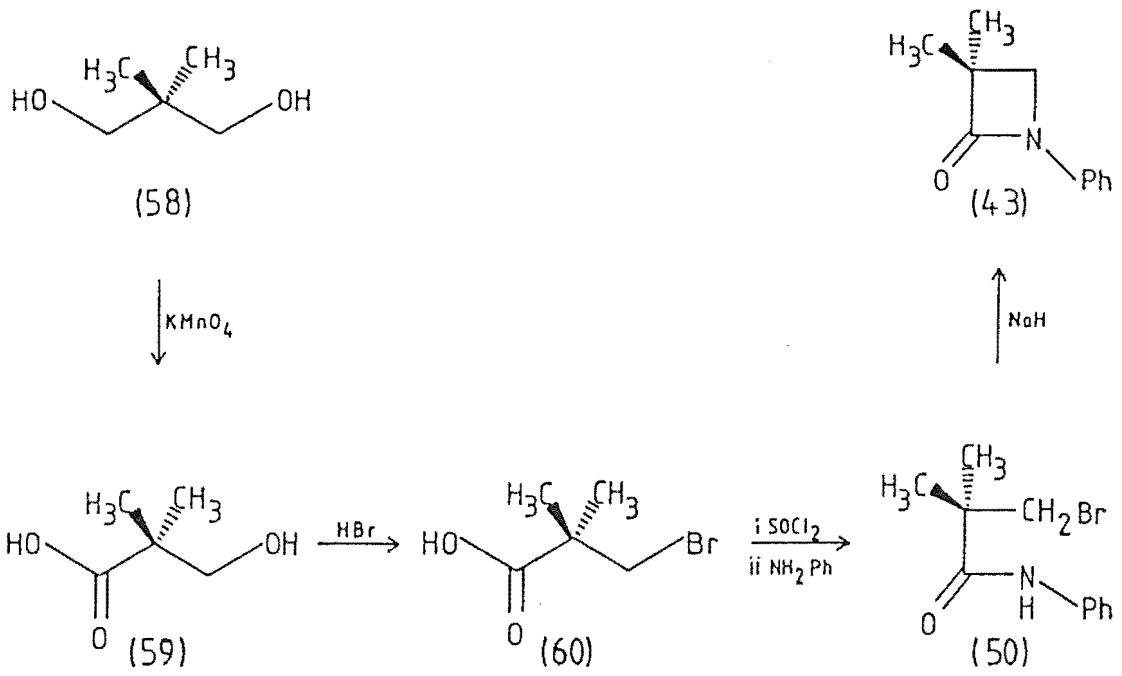
(56) (57) (49) (42)

Scheme 13

Reaction of dimethylpropanoic acid (56) with sulphuryl chloride, initiated by ultraviolet light, gave an oil which was shown by ^1H n.m.r. spectroscopic analysis, to contain starting material (56), the monochlorinated product (57) and dichlorinated products ca.2:2:1. The monochlorinated product (57) was separated from the mixture by spinning-band distillation. The chlorinated acid (57) was treated with thionyl chloride and subsequently with *t*-butylamine to give N-*t*-butyl-3-chloro-2,2-dimethylpropanamide (49).

Cylisation of the haloamide (49) was achieved by treatment with five molar equivalents of sodium hydride[26] in a mixture of dichloromethane and dimethylformamide (3:1). Analysis of the 1-*t*-butyl-3,3-dimethylazetidin-2-one (42) produced, showed the presence of water, even after repeated distillation and extensive drying under reduced pressure in the presence of phosphorus pentoxide. Hydration of other azetidin-2-ones has been reported.[27]

The azetidin-2-one (43) was synthesised from 2,2-dimethyl-1,3-propandiol (58) as shown in Scheme 14.

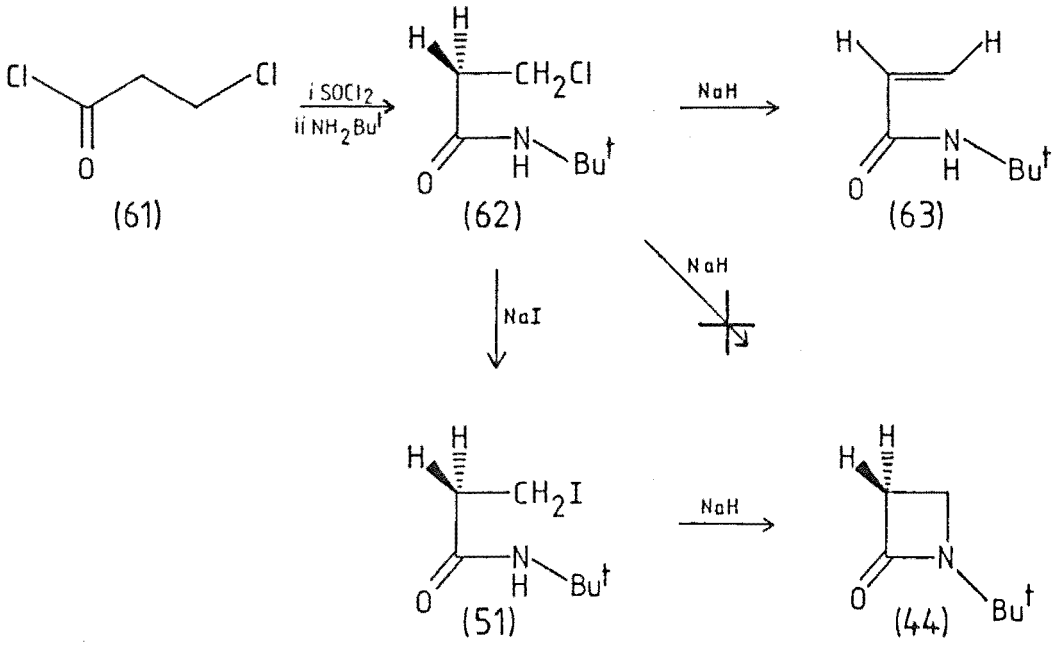


Scheme 14

Dimethyl-1,3-propandiol (58) was oxidised with potassium permanganate to give 3-hydroxy-2,2-dimethylpropanoic acid (59). The acid (59) was treated with 48% aqueous hydrobromic acid, and the resulting 3-bromopropanoic acid (60) was separated by steam distillation. The bromopropanoic acid (60) was treated with thionyl chloride, followed by aniline to give 3-bromo-2,2-dimethyl-N-phenylpropanamide (50).

The propanamide (50) cyclised upon treatment with 2.5 molar equivalents of sodium hydride in a mixture of dichloromethane and dimethylformamide (4:1) to give 3,3-dimethyl-1-phenylazetidin-2-one (43).

The azetidin-2-one (44) was prepared as outlined in Scheme 15. Treatment of 3-chloropropanoyl chloride (61) with *t*-butylamine gave N-*t*-butyl-3-chloropropanamide (62).



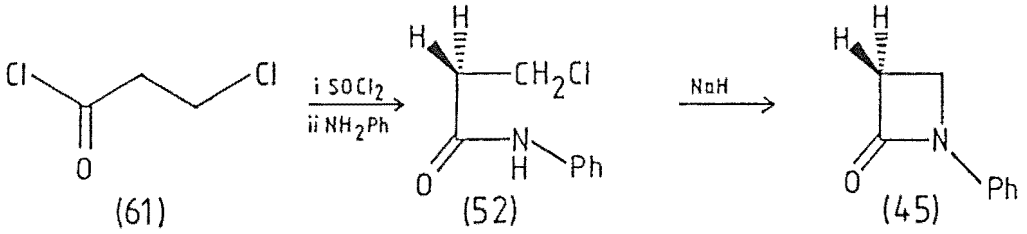
Scheme 15

The base-promoted reaction of the chloropropanamide (62) to give the azetidin-2-one (44) was expected to be in competition with reaction to give the acrylamide (63).[28] To limit acrylamide formation the procedure of Wasserman and co-workers[28] was used. The chloroamide (62) was added slowly to a dilute solution (0.1M) of sodium hydride in a mixture of dichloromethane and dimethylformamide (4:1). Despite these precautions none of the azetidin-2-one (44) was detected in the crude product mixture by ^{1}H n.m.r. The only product detected was the acrylamide (63).

Takahata and co-workers[29] have reported the cyclisation of haloamides using phase-transfer catalysts. Accordingly, the chloroamide (62) was treated with a solution of potassium hydroxide and tetra-*n*-butylammonium chloride in tetrahydrofuran. Analysis by ^{1}H n.m.r. of the crude product gave no indication of the formation of the azetidin-2-one (44).

Wasserman and co-workers[28] showed that the ratio of formation of azetidin-2-one to acrylamide is higher when an iodoamide is cyclised instead of a chloroamide. The chloroamide (62) was converted to the iodoamide (51) by treatment with sodium iodide in butan-2-ol. The crude iodoamide (51) was diluted to 0.05M with a solution of dichloromethane and dimethyl formamide (4:1), and added slowly to a solution of 0.05M sodium hydride in dichloromethane and dimethylformamide (4:1). Work up of the reaction including chromatography and distillation to separate the acrylamide (63) gave 1-*t*-butylazetidin-2-one (44). The azetidin-2-one (44) decomposed readily unless it was completely pure.

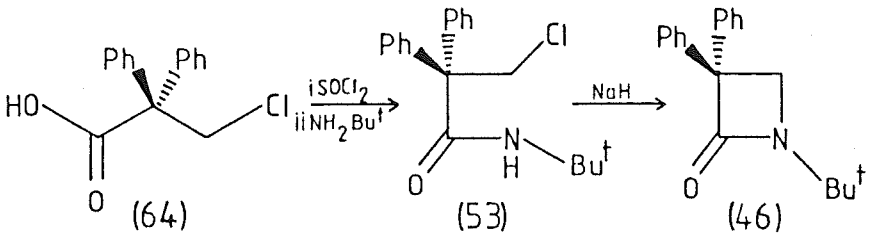
The azetidin-2-one (45) was synthesised as shown in Scheme 16.



Scheme 16

3-Chloropropanoyl chloride (61) was treated with aniline to give 3-chloro-N-phenylpropanamide (52). The chloroamide (52) was treated with sodium hydride in dilute solution to give 1-phenylazetidin-2-one (45).

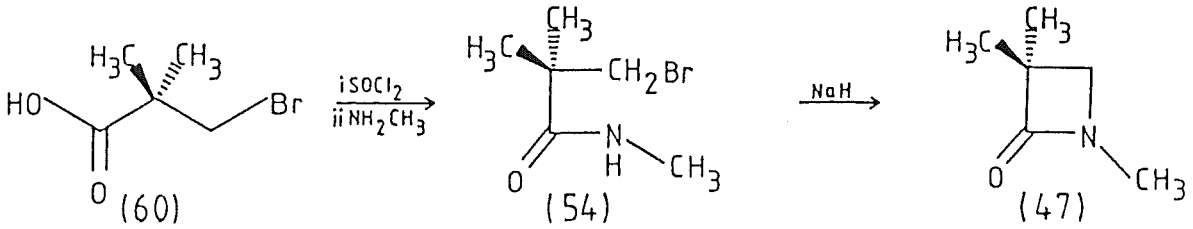
The azetidin-2-one (46) was synthesised from 3-chloro-2,2-diphenylpropanoic acid (64)[30] (Scheme 17).



Scheme 17

The chlorodiphenylpropanoic acid (64) was treated with thionyl chloride then *t*-butylamine to give N-*t*-butyl-3-chloro-2,2-diphenyl-propanamide (53). This propanamide (53) was treated with a total of fifteen molar equivalents of sodium hydride over sixteen hours to bring about cyclisation to give N-*t*-butyl-3,3-diphenylazetidin-2-one (46).

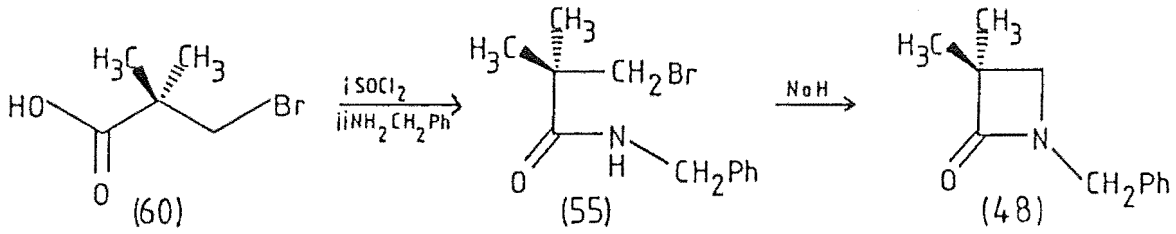
The azetidin-2-one (47) was prepared in a similar manner to the azetidin-2-one (43) as shown in Scheme 18.



Scheme 18

Treatment of 3-bromodimethylpropanoic acid (60) with thionyl chloride and subsequently with 25% aqueous methylamine gave 3-bromo-N,2,2-trimethylpropanamide (54). Cyclisation of the propanamide (54) with sodium hydride gave 1,3,3-trimethylazetidin-2-one (47).

In a similar manner the azetidin-2-one (48) was prepared from the 3-bromodimethylpropanoic acid (60), (Scheme 19).



Scheme 19

Treatment of the substituted propanoic acid (60) with thionyl chloride and subsequently with benzylamine gave N-benzyl-3-bromo-2,2-dimethylpropanamide (55). Cyclisation of the propanamide (55) by treatment with sodium hydride gave 1-benzyl-3,3-dimethylazetidin-2-one (48).

2.2 Reactions of the β-Lactams (42)-(48).

Free radical reactions of the β-lactams (42)-(48) were studied to investigate direct functionalisation of azetidin-2-ones at the C4 position. 1-*t*-Butyl-3,3-dimethylazetidin-2-one (42) was treated with sulphuryl chloride and benzoyl peroxide in carbon tetrachloride and irradiated with ultraviolet light.[31] Concentration of the mixture gave a crystalline material and an oil. ^{1}H n.m.r. analysis of the oil showed the presence of starting material (42). The crystalline material was insoluble in organic solvents but ^{1}H n.m.r. analysis in D_2O showed resonances associated with the azetidin-2-one (42). The crystalline material was dissolved in

dichloromethane and water. After treating with dilute sodium hydroxide, the dichloromethane layer was separated, dried and concentrated to give an oil with spectroscopic properties expected for the azetidin-2-one (42). It seems likely, therefore, that the crystalline material was the hydrochloride salt of the azetidin-2-one (42).

Reaction of the azetidin-2-one (42) with N-bromosuccinimide (NBS) gave a similar crystalline product which afforded starting material (42) upon treatment with dilute sodium hydroxide. This would be consistent with formation of the hydrobromide salt of the azetidin-2-one (42).

To avoid salt formation, reactions with a non-halogenating reagent, *t*-butyl perbenzoate, were studied. The mechanism of reaction of organic substrates with *t*-butyl perbenzoate in the presence of a copper salt catalyst has been investigated.[32] A free-radical chain process has been proposed which involves generation of *t*-butoxy radical by a one-electron reduction of the perester(i) (Scheme 20). Hydrogen-atom abstraction from the organic substrate by *t*-butoxy radical affords the substrate radical (ii). Interaction of this radical with the cupric carboxylate produces the ester and regenerates the original copper species (iii).

t- BuOOCOPh + Cu^{I} → t-BuO· + $^{-}$OCOPh + Cu^{II} (i)

t- BuO· + R-H → R· + t- BuOH (ii)

R· + $^{-}$OCOPh + Cu^{II} → ROCOPh + Cu^{I} (iii)

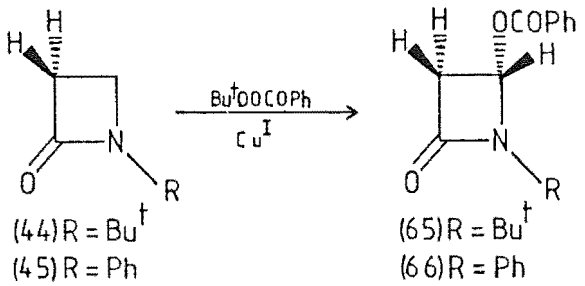
Scheme 20

1-t-Butylazetidin-2-one (44) was treated with t- butyl perbenzoate in the presence of a catalytic amount of cupric octanoate in benzene. Chromatography of the product mixture afforded 4-benzoyloxy-1-t- butylazetidin-2-one (65) (59%) (Scheme 21) and recovered starting material (44) (39%).

Assignment of the structure of azetidin-2-one (65) as the C4-substituted product is based on ^{1}H n.m.r. data. Barrow and Spotswood[33] have reported ^{1}H n.m.r. data for a variety of C3 and C4-substituted azetidin-2-ones. They reported that a substituent at C3 or C4 induces magnetic non-equivalence in the neighbouring methylene group. For methylene protons at C3 the geminal coupling constant ranges from 14.3 - 15.0 Hz. For methylene protons at C4 the geminal coupling ranges from 4.9-5.9 Hz. The observed methylene group geminal coupling of 14 Hz in the ^{1}H n.m.r. spectra of the product of the reaction of the azetidin-2-one (44) indicates that substitution has occurred at C4.

Similar treatment of 1-phenylazetidin-2-one (45) with t- butyl perbenzoate gave 4-benzoyloxy-1-phenylazetidin-2-one (66) (Scheme 21). Again the product is assigned as the C4 substituted compound on the basis of a coupling

constant of 16Hz, attributed to the geminal coupling of the methylene protons at C3.

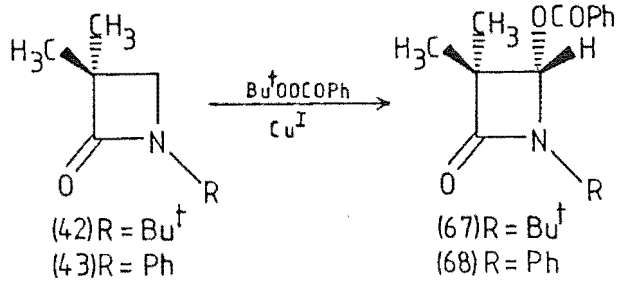


Scheme 21

The incorporation of a benzoyloxy substituent at C4 in the azetidin-2-ones (44) and (45) indicates that the C4 methylene is more reactive than the C3 methylene group, to hydrogen-atom abstraction by *t*-butoxy radicals. Presumably this reflects the activating effect of the amide nitrogen. A radical generated at C4 is expected to be stabilised through interaction of the radicals semi-occupied p-orbital with the amide Π-orbitals.

Reaction of the β-lactams (42) and (43), with methyl substituents at C3, were also examined. Treatment of 1-*t*-butyl-3,3-dimethylazetidin-2-one (42) with *t*-butyl perbenzoate gave 4-benzoyloxy-1-*t*-butyl-3,3-dimethyl-azetidin-2-one (67).

Treatment of 3,3-dimethyl-1-phenylazetidin-2-one (43) with *t*-butyl perbenzoate gave 4-benzoyloxy-3,3-dimethyl-1-phenylazetidin-2-one (68) (Scheme 22).



Scheme 22

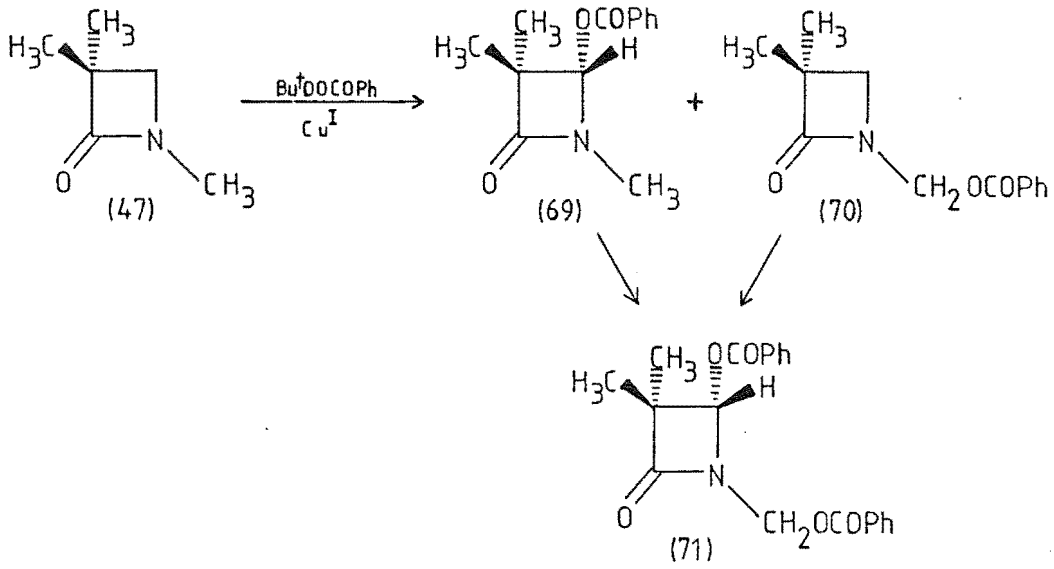
The rate of formation of the benzoyloxy-substituted β-lactams (67) and (68), in the reactions of the corresponding β-lactams (42) and (43), was considerably slower than the rate of formation of (65) and (66), in the reactions of the respective β-lactams (44) and (45). This indicates that substituents at C3 reduce the reactivity at C4. Presumably this is a steric effect.

In accord with the observed reduction in reaction rate on the introduction of methyl groups at C3, attempted reaction of the more hindered 3,3-diphenyl derivative (46) resulted in the isolation of starting material only. This can be attributed to the greater steric hindrance to reaction at C4 due to the bulky C3-phenyl substituents.

In order to examine the relative reactivity of C-H bonds α to amide nitrogen in endocyclic positions (C4) and in exocyclic positions (N-methyl,C-H bonds), the reaction of the β-lactam (47) was investigated. The exocyclic methyl substituent and the endocyclic C4-methylene will both be activated to hydrogen-atom abstraction by *t*-butoxy radical, through interaction

with the amide nitrogen.

Treatment of 1,3,3-trimethylazetidin-2-one (47) with *t*-butyl perbenzoate gave three products, the 4-benzoyloxy-substituted azetidin-2-one (69), the benzoyloxymethylazetidin-2-one (70), and the disubstituted azetidin-2-one (71) (Scheme 23).



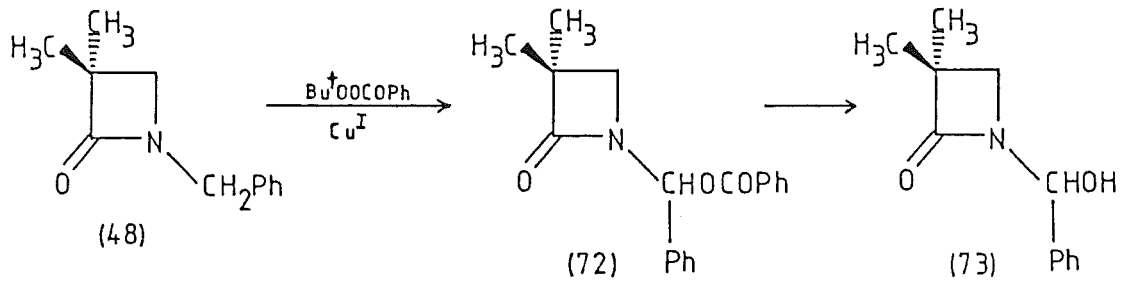
Scheme 23

Anaylsis of reaction mixtures by ^{1}H n.m.r. after short reaction times showed that the azetidin-2-ones (69) and (70) were the primary products of reaction of the azetidin-2-one (47) with *t*-butyl perbenzoate. The ratio of the endocyclic substitution product (69) to the exocyclic substitution product (70) was ca. 1:2. After more extensive reaction, the disubstituted product (71) was produced through subsequent reaction of the azetidin-2-ones (69) and (70).

The ratio of the primary products (69) and (70) indicates that the exocyclic carbon α to nitrogen in the

β-lactam (47) is marginally more reactive than the endocyclic carbon α to nitrogen. Presumably the strain associated with formation of the endocyclic radical outweighs the normal thermodynamic preference for the production of secondary radicals relative to primary radicals.

Treatment of 1-benzyl-3,3-dimethylazetidin-2-one (48) with *t*-butyl perbenzoate gave, after chromatography, 3,3-dimethyl-1-(α-hydroxybenzyl)-azetidin-2-one (73) (Scheme 24).



Scheme 24

Analysis of the crude reaction product by ^{1}H n.m.r. indicated the presence of the benzoyloxy-substituted β-lactam (72), but the material hydrolysed during chromatography to give the alcohol (73). The reaction of β-lactam (48) with *t*-butyl perbenzoate occurs solely at the exocyclic carbon α to nitrogen because the benzylic protons are highly activated to hydrogen-atom abstraction by *t*-butoxy radical.

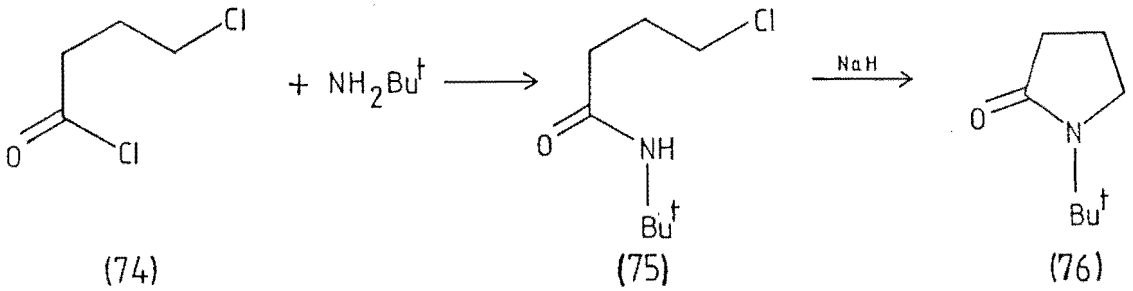
CHAPTER 3

Results and Discussion

Functionalisation of γ-Lactams at the C5 Position

3.1 Preparation of γ-Lactams.

To investigate functionalisation of γ-lactams at C5 samples of (76), (78) and (80) were required. The pyrrolidin-2-one (76) was synthesised as shown in Scheme 25.

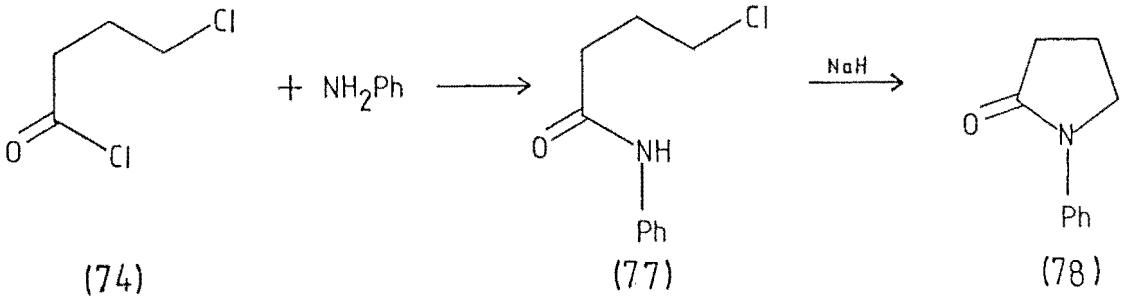


(74) (75) (76)

Scheme 25

4-Chlorobutanoyl chloride (74) was treated with *t*- butylamine to give N-*t*- butyl-4-chlorobutanamide (75). The chloroamide (75) cyclised upon treatment with sodium hydride to give 1-*t*-butylpyrrolidin-2-one (76).

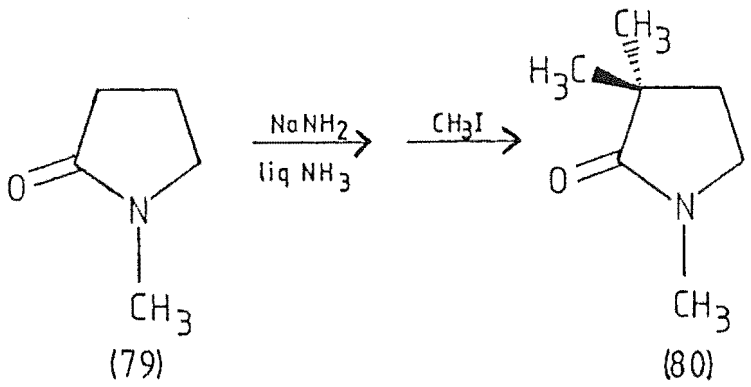
The pyrrolidin-2-one (78) was prepared as shown in Scheme 26. Treatment of 4-chlorobutanoyl chloride (74) with aniline gave 4-chloro-N-phenylbutanamide (77). The chloroamide (77) was treated with sodium hydride to give 1-phenylpyrrolidin-2-one (78).



(74) (77) (78)

Scheme 26

Gassman and Fox[34] have reported the synthesis of 1,3,3-trimethylpyrrolidin-2-one (80) as shown in Scheme 27.

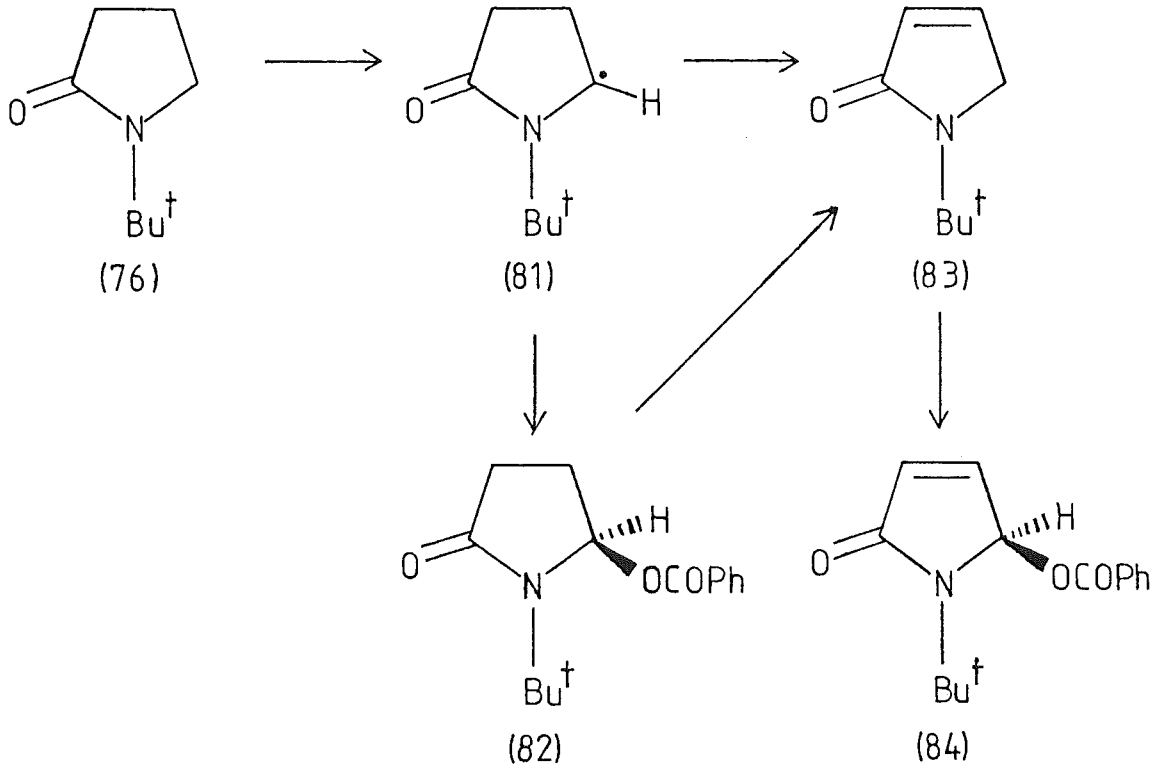


Scheme 27

Accordingly, 1-methylpyrrolidin-2-one (79) was treated with sodium amide in liquid ammonia and subsequently with methyl iodide, to give 1,3,3-trimethylpyrrolidin-2-one (80).

3.2 Reaction of γ-lactams with *t*-butyl perbenzoate.

Treatment of 1-*t*-butylpyrrolidin-2-one (76) with *t*-butyl perbenzoate gave an oil that contained none of the C5 benzoyloxylated material (82) (Scheme 28) as shown by ^{1}H n.m.r. analysis. The oil decomposed rapidly to give a dark brown amorphous solid. The original oil gave rise to ^{1}H n.m.r. signals at δ6.13 (d, J=6Hz), 6.83 (d, J=2Hz) and 7.03 ppm (dd, J=2, 6Hz) in the ratio 1:1:1. This is consistent with the formation of compound (84) (Scheme 28).



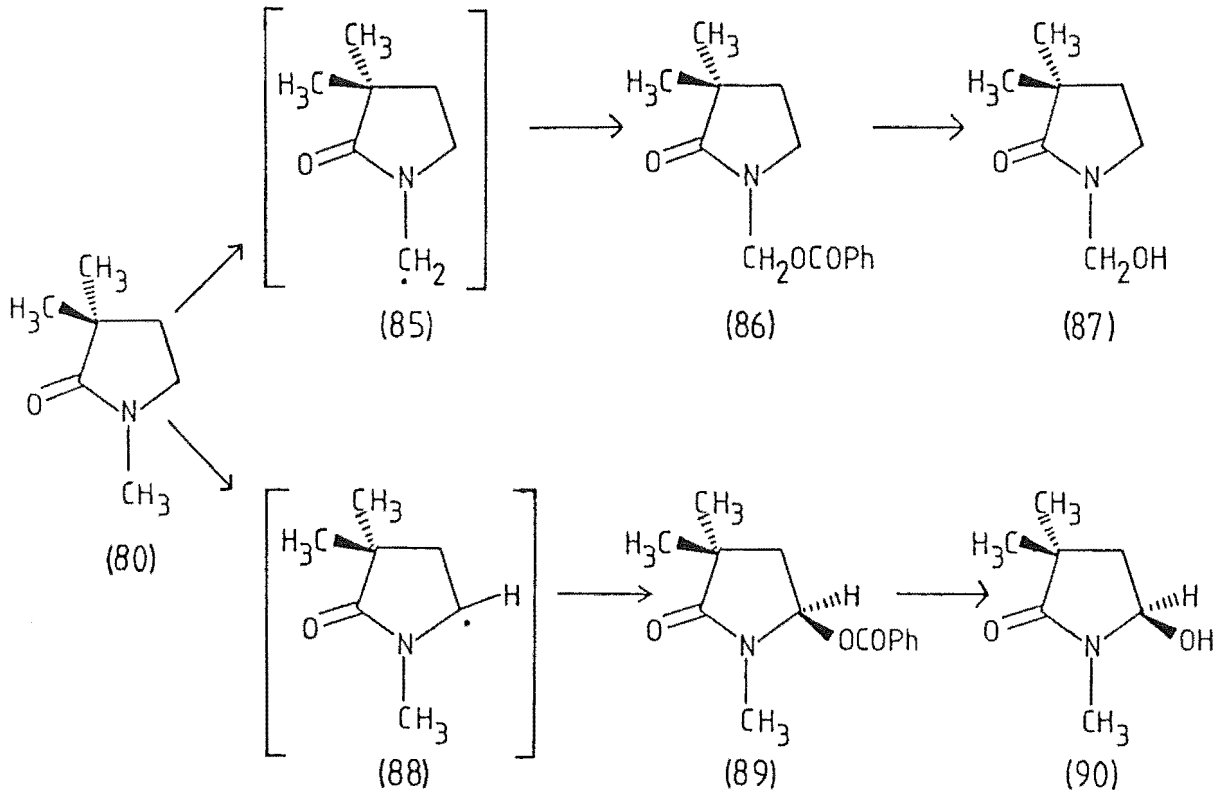
Scheme 28

Formation of (84) can be attributed to direct reaction of the intermediate radical (81) to give the aromatic compound (83), or to elimination of the benzoate (82) to give (83), with subsequent benzoyloxylation of (83) to give (84). Reactions analogous to the interconversion of (82) to (83) have been reported previously.[35] The chemical shifts of the ^{1}H n.m.r. signals attributed to (84) are consistent with those reported by Lightner and Pak[36] for a related compound.

Owing to extensive decomposition, the reaction mixture could not be characterised further and pure products were not isolated. There have been reports of compounds analogous to (84) undergoing rapid dimerisation reactions.[35]

The crude reaction mixture from reaction of 1-phenylpyrrolidin-2-one (78) with *t*-butyl perbenzoate contained no C5 benzoyloxylated material as shown by ^{1}H n.m.r. analysis. The reaction was not investigated further.

The reaction of 1,3,3-trimethylpyrrolidin-2-one (80) with *t*-butyl perbenzoate was studied to investigate the effect of substituents in preventing the formation of compounds analogous to (83). The reaction gave, after chromatography, 1-hydroxymethyl-3,3-dimethylpyrrolidin-2-one (87) and 5-hydroxy-1,3,3-trimethylpyrrolidin-2-one (90) (Scheme 29).



Scheme 29

Analysis of the crude reaction mixture by ^{1}H n.m.r. spectroscopy indicated the presence of the two benzoyloxy

substituted pyrrolidin-2-ones (86) and (89), but the materials hydrolysed during chromatography to the respective alcohols (87) and (90). Analysis of the crude reaction mixture showed that the ratio of the exocyclic substitution product (86) to the endocyclic substitution product (89) was ca. 1:4. The ratio of the two benzoyloxy substituted pyrrolidin-2-ones (86) and (89) indicates that the endocyclic position α to nitrogen is more reactive than the exocyclic position α to nitrogen. Presumably the γ-lactam ring is sufficiently flexible that geometrical constraints on the transition state of the reaction leading to the endocyclic radical (88) do not outweigh the normal thermodynamic preference for the production of the secondary endocyclic radical (88), compared to the primary exocyclic radical (85).

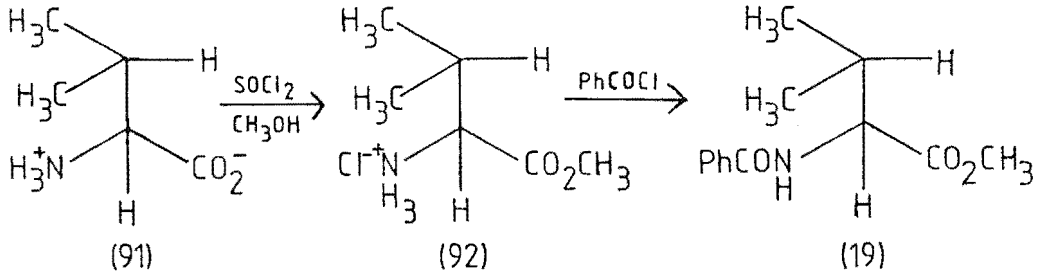
CHAPTER 4

Results and Discussion

Functionalisation of a Valine Derivative at the C3 Position

Page

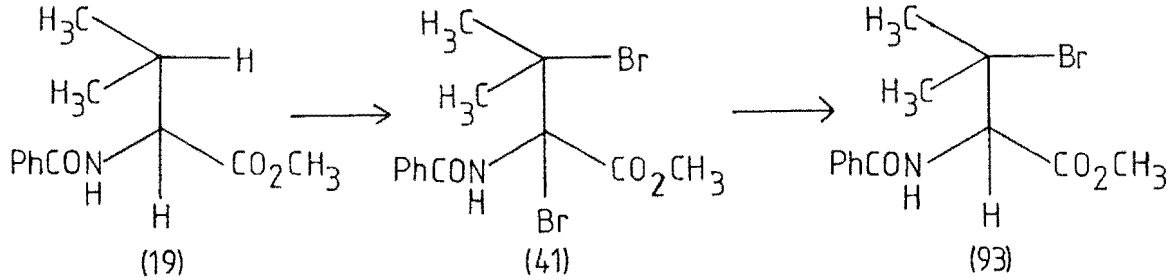
N-Benzoylvaline methyl ester (19) was prepared by the method of Applewhite and co-workers.[37] Treatment of D,L-valine(91) with thionyl chloride in methanol gave the valine methyl ester (92). The ester (92) was treated with benzoyl chloride to give N-benzoylvaline methyl ester (19) (Scheme 30).



(91) (92) (19)

Scheme 30

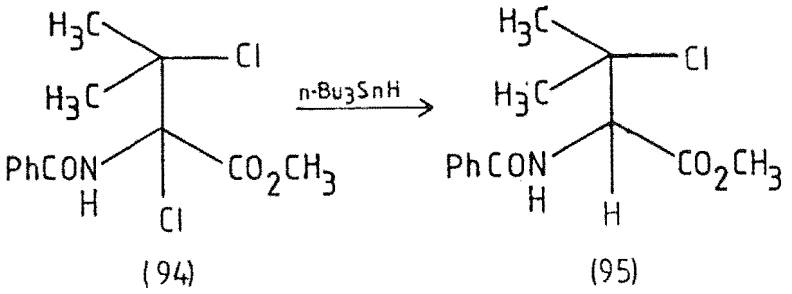
It was hoped that regioselective incorporation of bromine at the C3 position of (19) could be achieved through the known reaction of (19) with N-bromosuccinimide (NBS) to give the dibromovaline derivative (41), followed by selective reduction of the bromide at the α-position to give (93) (Scheme 31).



(19) (41) (93)

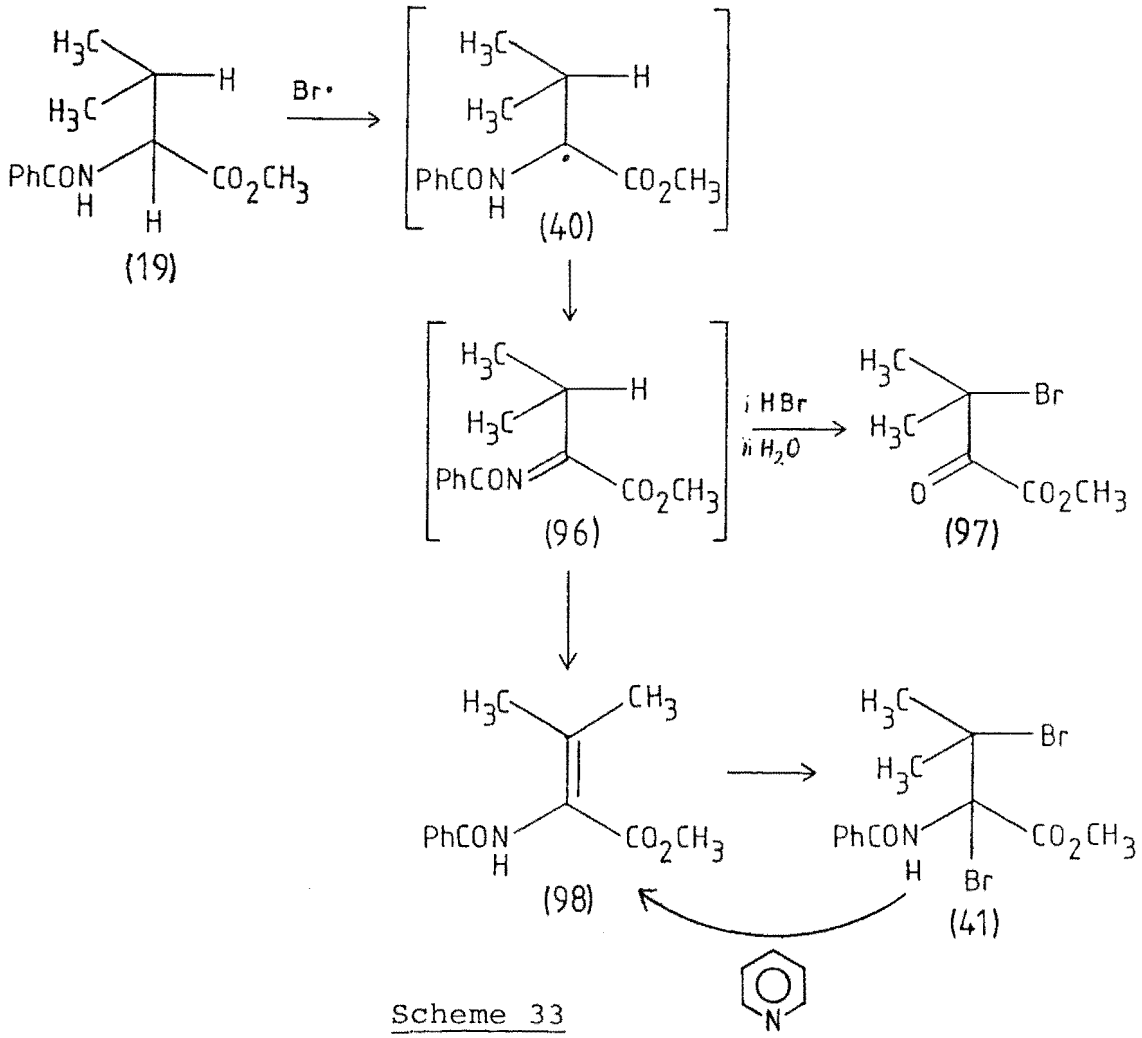
Scheme 31

Reaction of the dichlorovaline derivative (94) with tri-*n*-butyltin hydride to give the β-chlorovaline derivative (95) has been reported[25] (Scheme 32).



Scheme 32

The reaction of N-benzoylvaline methyl ester (19) with 2.5 or less molar equivalents of NBS afforded methyl 3-bromo-3-methyl-2-oxobutanoate (97). Formation of this product can be attributed to reaction of (19) by hydrogen-atom transfer from the α-position to give the radical (40), subsequent reaction of (40) to give (96), and reaction of (96) with hydrogen bromide to give (97) (Scheme 33).

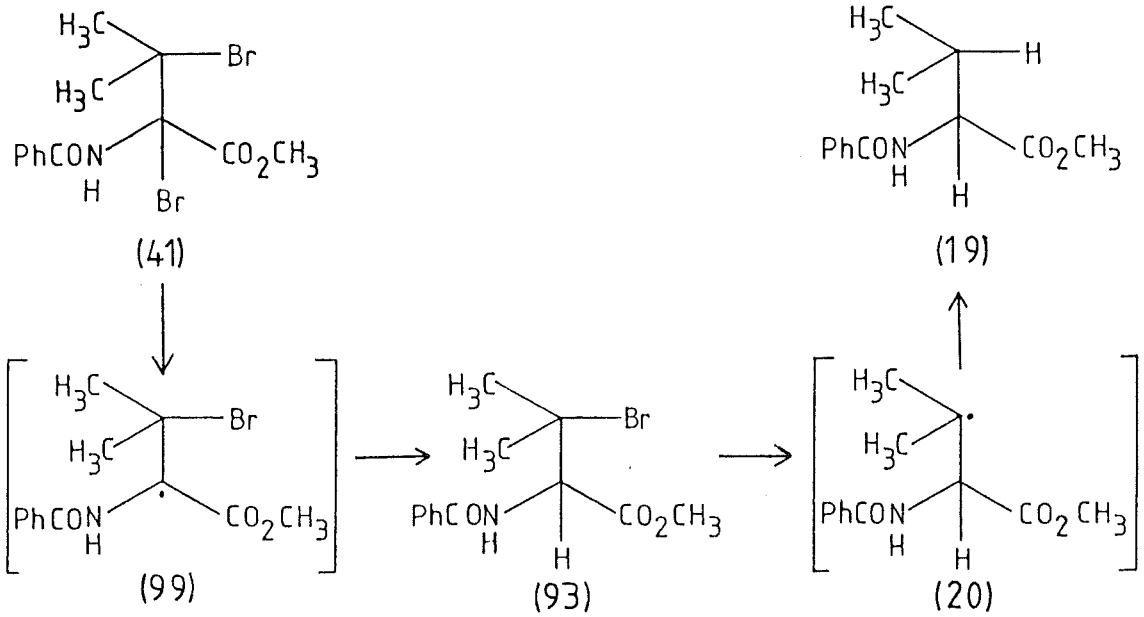


Scheme 33

To avoid formation of (97) in the reaction of (19) with NBS an excess of NBS was used, since NBS is known to be a scavenger for hydrogen bromide.[38] Reaction of N-benzoylvaline methyl ester (19) with 3 or more molar equivalents of NBS gave the dibromovaline derivative (41). Presumably in the absence of hydrogen bromide, (96) undergoes tautomerism to give (98) which reacts by the addition of bromine to give (41) (Scheme 33).

Treatment of the crude dibromovaline derivative (41) with pyridine gave Methyl 2-benzamido-3-methylbutanoate (98) (Scheme 33). Given that the dibromovaline derivative (41), is produced by reaction of (98) with NBS,[39] then the debromination of (41) provides a method for storing the unstable functionalised valine derivative (41).

Reaction of the dibromovaline derivative (41) with tri-*n*-butyltin hydride gave N-benzoyl-3-bromovaline methyl ester (93) and (19) in the ratio ca. 7.7:1 as shown by HPLC analysis. Presumably, formation of N-benzoylvaline methyl ester (19) is the result of subsequent reaction of the monobromovaline derivative (93) (Scheme 34).



Scheme 34

In the reaction of the dibromovaline derivative (41) with tri-*n*-butyltin hydride, the stability of the initial free radical intermediate is the prime factor in determining the regioselectivity of the halogen atom abstraction.[40] Abstraction of the bromine atom from the α- position of (41) is favoured because the α-centered radical (99) is a captodative radical, stabilised by the resonance electron-donating amido and electron-withdrawing carboxy groups.

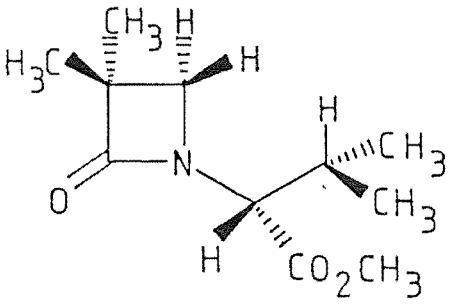
CHAPTER 5

Results and Discussion

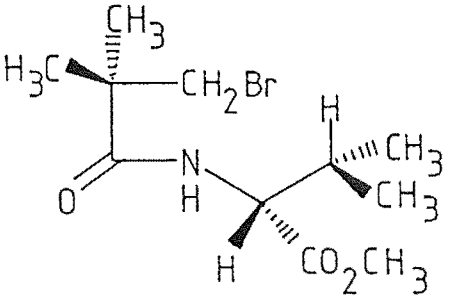
Approaches to Bicyclic β-Lactams Through Reactions of 1-(1-Methoxycarbonyl-2-methylpropyl)-3,3-dimethylazetidin-2-one (31) and N-(3-Bromo-2,2-dimethylpropanoyl)valine Methyl Ester (100).

5.1 Preparation of the Substrates (31) and (100).

The azetidin-2-one (31) and the acyclic substrate (100) were synthesised in order to investigate their use in the formation of bicyclic β-lactams.



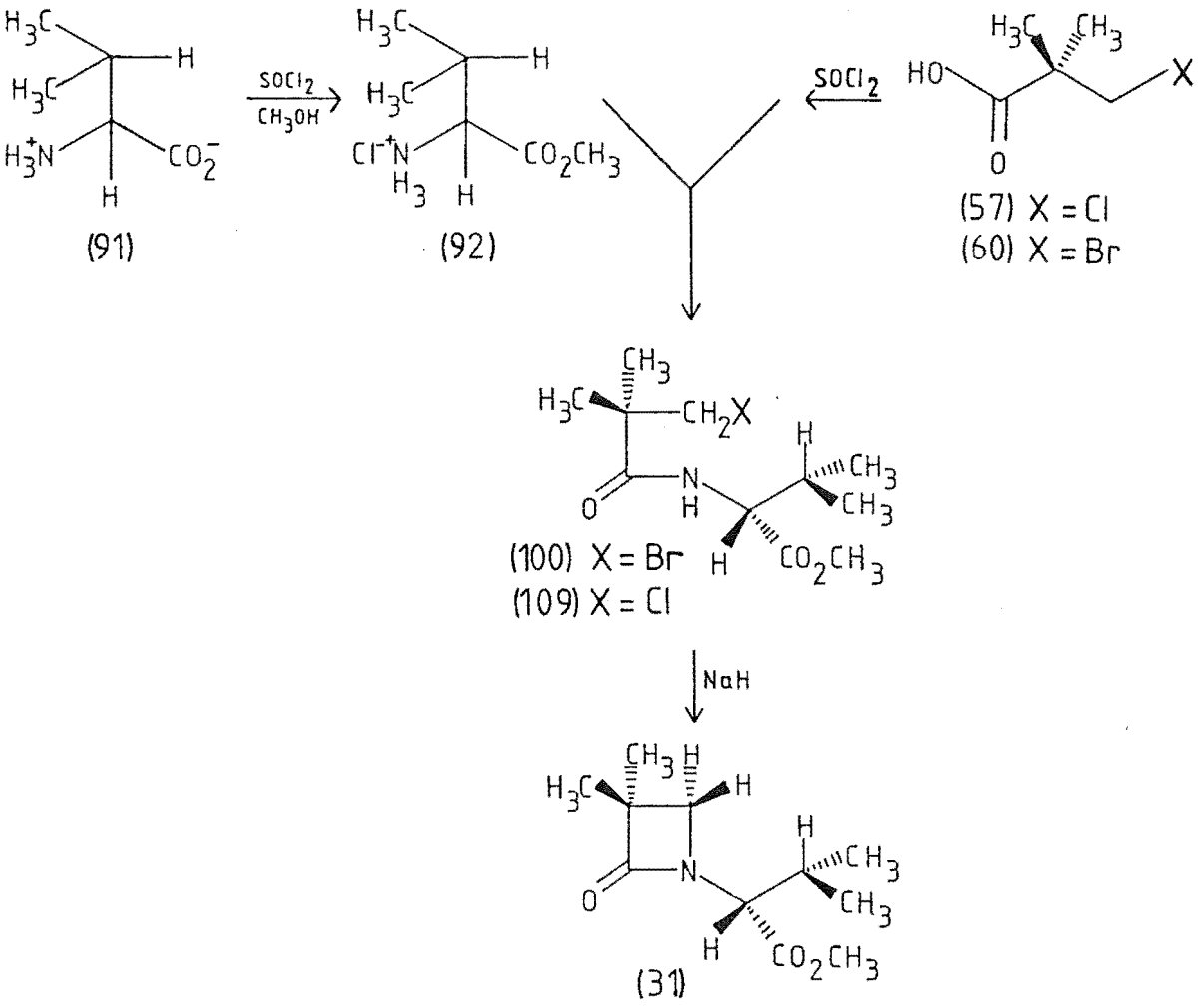
(31)



(100)

3-Bromo-2,2-dimethylpropanoic acid (60) was treated with thionyl chloride and subsequently with the valine methyl ester (92) under basic conditions to give N-(3-bromo-2,2-dimethylpropanoyl)valine methyl ester (100).

3-Chloro-2,2-dimethylpropanoic acid (57) was treated with thionyl chloride and subsequently with the valine methyl ester (92) under basic conditions to give N-(3-chloro-2,2-dimethylpropanoyl)valine methyl ester (109). Cyclisation of (109) by treatment with sodium hydride gave 1-(1-methoxycarbonyl-2-methylpropyl)-3,3-dimethylazetidin-2-one (31) (Scheme 35).

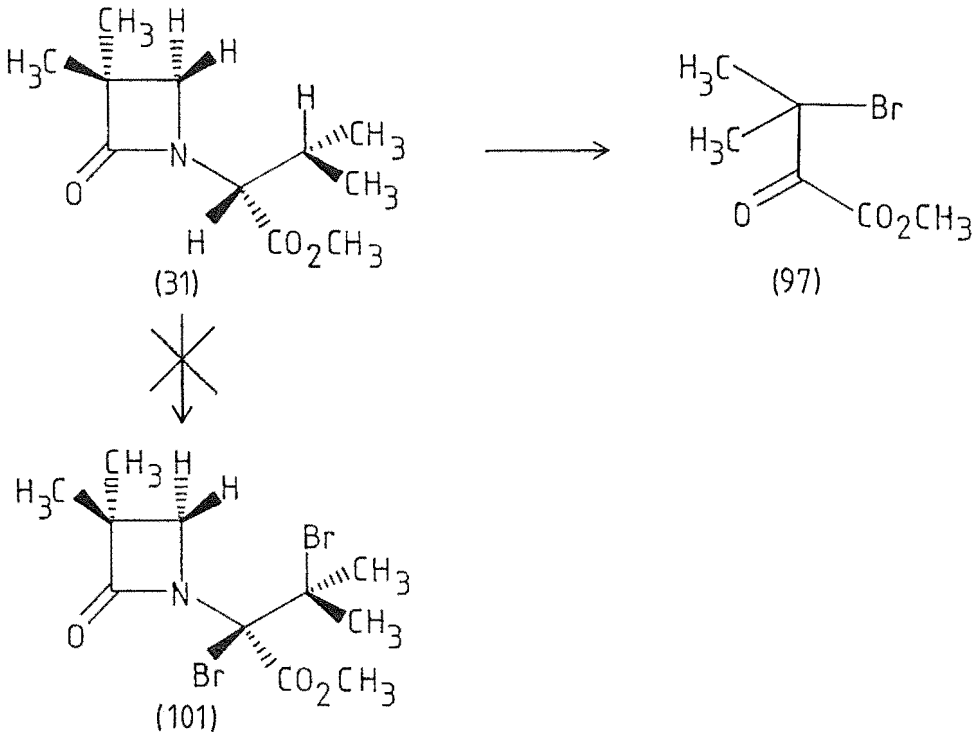


Scheme 35

5.2 Reactions of the Substrates (31) and (100).

Treatment of the azetidin-2-one (31) with *t*-butyl perbenzoate did not result in reaction of (31), as shown by ^{1}H n.m.r. analysis. Chromatography of reaction mixtures lead to 95% recovery of the azetidin-2-one (31). Analysis of models of (31) shows that the β-lactam C4 protons are shielded by the methyl substituents at C3 and by the N-substituent, and they are unlikely to be abstracted by a *t*-butoxy radical.

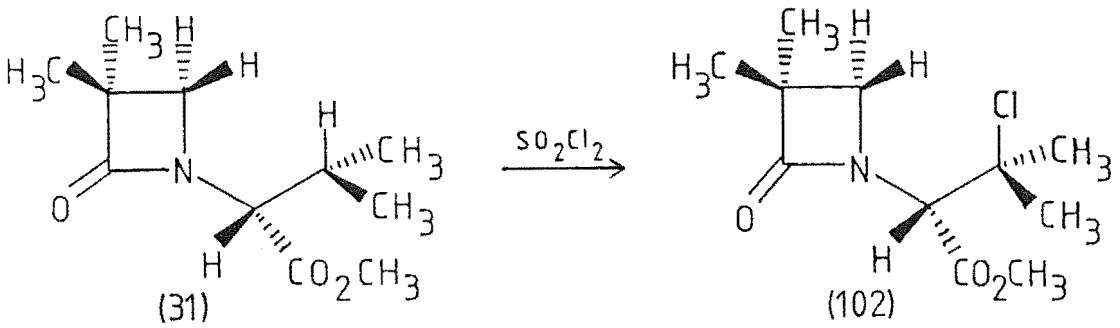
The azetidin-2-one (31) was treated with NBS. ^{1}H n.m.r. analysis of the reaction mixture showed formation of the β-keto ester (97) (Scheme 36). The dibromo-derivative (101) was not detected, even when excess NBS was used.



Scheme 36

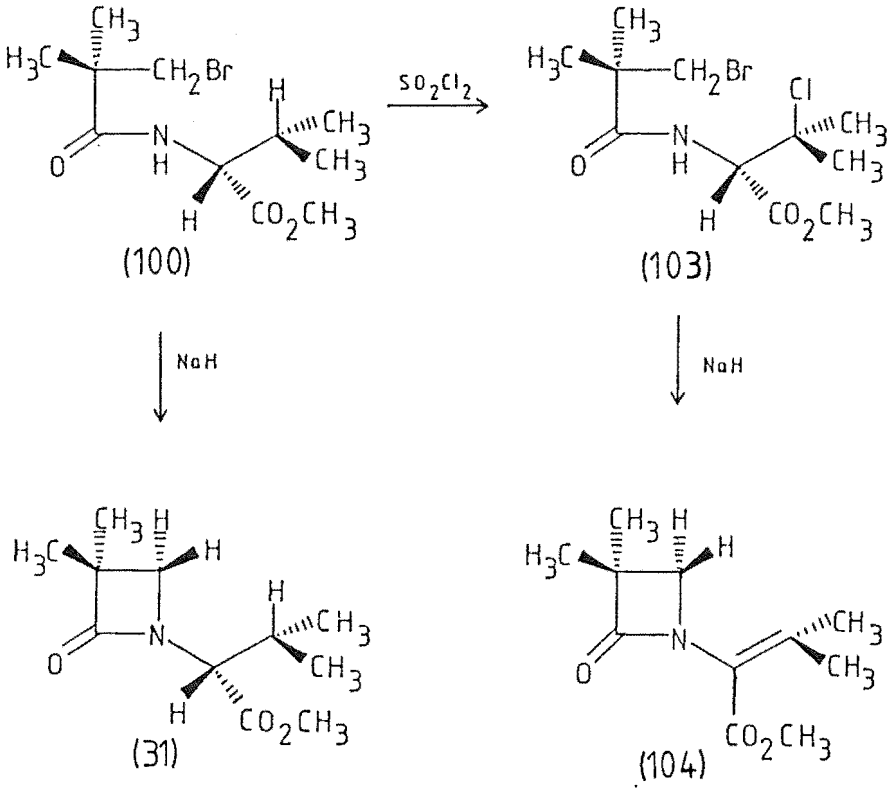
Treatment of the azetidin-2-one (31) with sulphuryl chloride gave a complex mixture of products. Analysis of reaction mixtures by HPLC and ^{1}H n.m.r. indicated formation of the β-chlorosubstituted azetidin-2-one (102) (Scheme 37), by comparison with an authentic sample (see below). The chlorinated azetidin-2-one (102) was not separated from other products in the reaction mixtures.

Reactions of N-(3-bromo-2,2-dimethylpropanoyl)valine methyl ester (100) were studied to investigate the possibility of valine functionalisation prior to formation of the



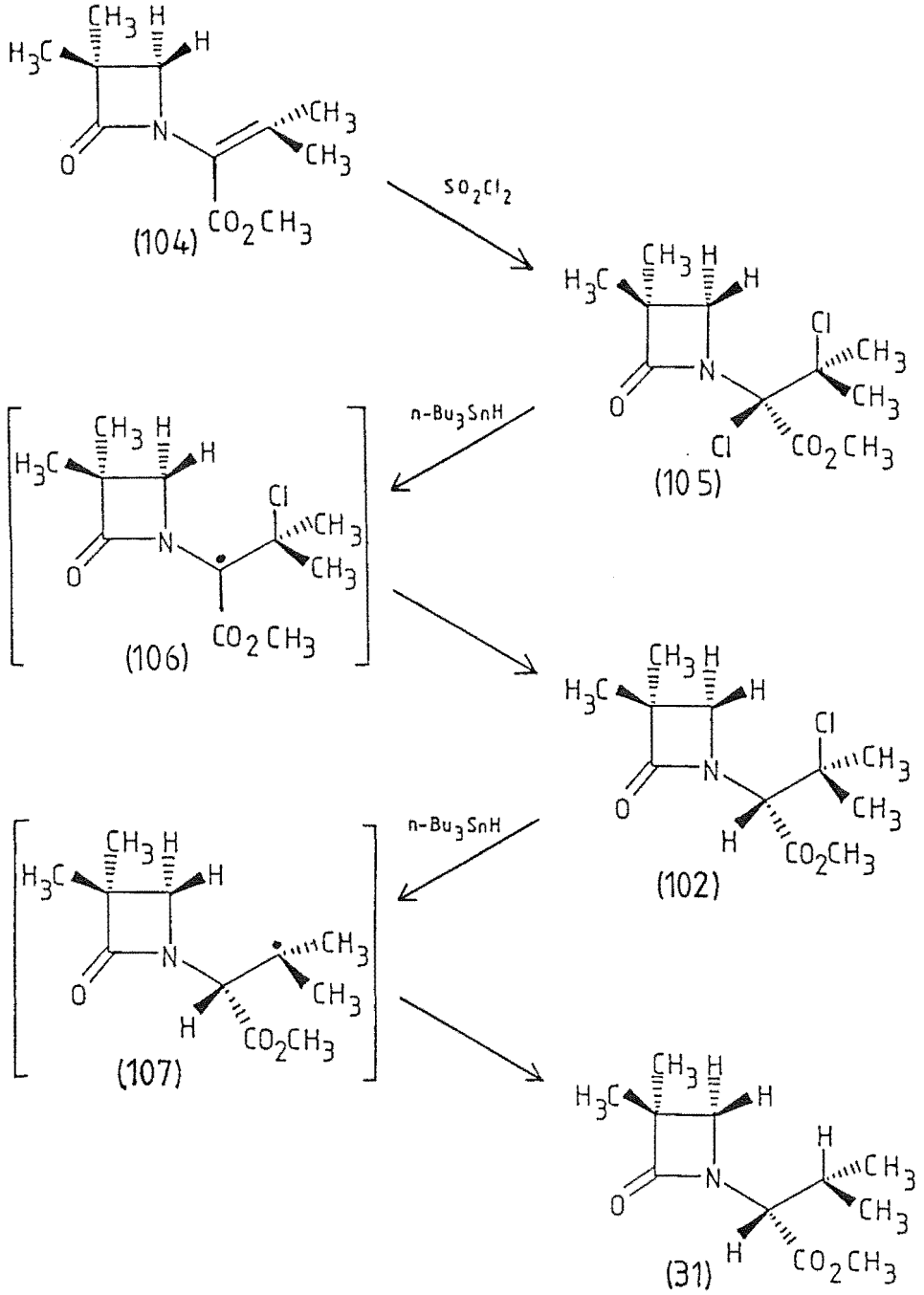
Scheme 37

β-lactam ring. Treatment of the bromopropanoylvaline derivative (100) with sulphuryl chloride, with reaction initiated using benzoyl peroxide, gave N-(3-bromo-2,2-dimethylpropanoyl)-3-chlorovaline methyl ester (103). The extent of reaction was monitored by ^{1}H n.m.r. so that formation of secondary chlorinated products could be prevented. The crude product mixture was treated with sodium hydride to give a mixture of the azetidin-2-one (31) and 1-(1-methoxycarbonyl-2-methylprop-1-enyl)-3,3-dimethyl azetidin-2-one (104) (Scheme 38). The two azetidin-2-ones were separated by chromatography. Presumably (104) is produced by treatment of the β-chlorovaline derivative (103) with sodium hydride which involves hydrogen chloride elimination as well as the base-promoted cyclisation to give the β-lactam ring. Formation of the azetidin-2-one (31) is the result of reaction of the non-chlorinated material (100).



Scheme 38

Treatment of (104) with sulphuryl chloride gave 1-(2,3-dichloro-1-methoxycarbonyl-2-methylpropyl)-3,3-dimethyl azetidin-2-one (105). The crude product mixture was treated with tri-*n*- butyltin hydride to give, after chromatography, 1-(3-chloro-1-methoxycarbonyl-2-methypropyl) -3,3-dimethylazetidin-2-one (102) and the azetidin-2-one (31) (Scheme 39). The ratio of (102) to (31) in the crude product mixture was shown by HPLC to be ca. 5:1. Presumably (31) is produced by subsequent reduction of (102).



Scheme 39

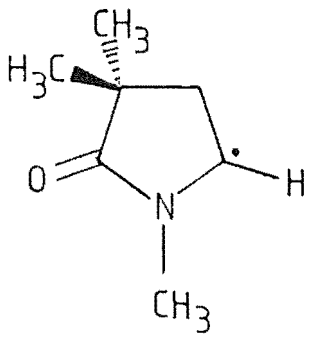
The abstraction of the chlorine atom from the α-position of (105) is favoured because the α-centred radical (106) is stabilized by the combined effects of the resonance electron-donating amido and electron-withdrawing carboxy groups.

CHAPTER 6.

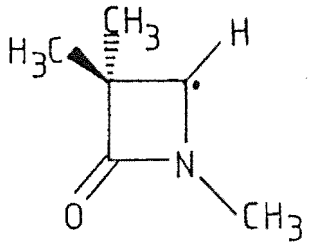
CONCLUSION

Reactions of β-lactams with *t*-butyl perbenzoate resulted in direct functionalisation of the azetidin-2-one ring at the C4 position. The rate of benzoyloxylation of β-lactams at the C4 position was less with C3-disubstituted β-lactams. There was no evidence for reaction of the β-lactams at the C3 position, but reaction at the exocyclic carbon adjacent to the amide nitrogen occured in competition with or, instead of, endocyclic functionalisation, in suitably substituted β-lactams.

Treatment of 1,3,3-trimethylpyrrolidin-2-one (80) with *t*-butyl perbenzoate resulted in substitution at the endocyclic carbon α to the amide nitrogen and at the exocyclic carbon α to the amide nitrogen. The relative reactivity at the endocyclic carbon α to nitrogen compared to the exocyclic carbon was greater for the γ-lactam (80) than for the corresponding β-lactam (47). Presumably this reflects the greater ease of formation of the radical (88) compared to (108). The change in hybridisation accompanying



(88)

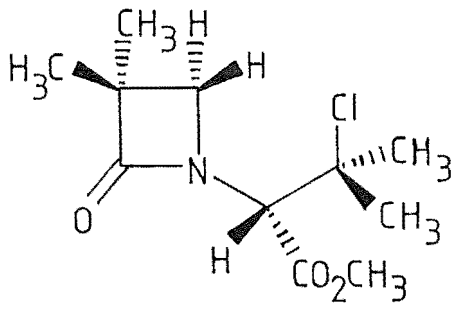


(108)

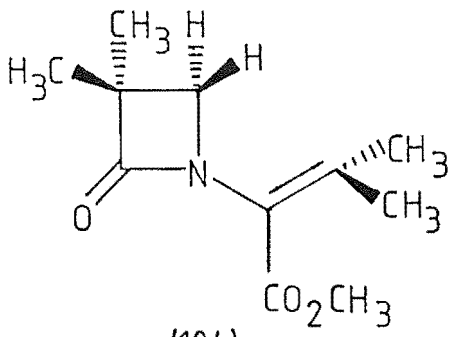
radical formation will engender greater strain in the radical (108) than in (88), and will relieve considerable gauche interactions in the formation of the radical (88).

Reaction of the valine derivative (19) with NBS, and treatment of the product with tri-*n*-butyltin hydride resulted in the regioselective bromination of the valine derivative (19) at the C3 position, to give (93).

Attempts to apply these results to the synthesis of bicyclic β-lactams were carried out using 1-(1-methoxycarbonyl-2-methylpropyl)-3,3-dimethylazetidin-2-one (31) and N-(3-bromo-2,2-dimethylpropanoyl)valine methyl ester (100). The azetidin-2-ones (102) and (104) were produced, which have the N-substituent suitably functionalised for elaboration to bicyclic compounds.



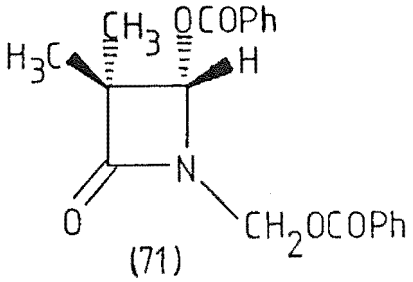
(102)



(104)

Functionalisation of the azetidin-2-one (31) at the C4 position was not achieved. One avenue for the continuation of this work would be the elaboration of the

disubstituted β-lactam (71) to produce bicyclic compounds.



(71)

EXPERIMENTAL

GENERAL

Infrared spectra were recorded on either a Shimadzu IR-27G or a Pye Unicam SP3-300 infrared spectrophotometer using potassium bromide plates, or as liquid films where indicated.

^{1}H Nuclear magnetic resonance (^{1}H n.m.r.) spectra were recorded in deuterochloroform or carbon tetrachloride, using tetramethylsilane as an internal reference, on a Varian T-60 nuclear magnetic resonance spectrometer operating at 60 MHz, or where stated on a Varian XL-300 nuclear magnetic resonance spectrometer operating at 300 MHz.

Melting points were determined in open tubes on an 'Electrothermal' melting point apparatus and are uncorrected.

Micro analyses were carried out by the microanalytical laboratory, University of Otago.

Mass spectra were recorded on either an AEI MS902 or a Hewlett Packard 5982A spectrometer.

Unless otherwise stated, preparative chromatography was carried out utilising a Chromatotron (a preparative, centrifugally accelerated, radial thin layer chromato-

graphy, Model 7924, Harrison Research Inc.), equipped with rotors coated with silica gel PF-254 (with $CaSO_4.\frac{1}{2}H_2O$ type 60 for TLC Merck 7749) of varying thickness (generally 1 or 2 mm).

HPLC was carried out on a Shimadzu LC-4A high performance liquid chromatograph, fitted with a UV spectrophotometer detector SPP2AS with a Hewlett Packard integrator 3390A. Analytical HPLC was carried out using a Dupont Zorbax cyanopropyl column, 25cm x 4.6mm i.d. (PN 880952-705). Preparative HPLC was carried out using a Dupont Zorbax cyanopropyl column, 25cm x 9.4 mm i.d. (PN 850952-205). The solvent system used was propan-2-ol -hexane (4,7, or 10% propan-2-ol).

The reagents and solvents used were of standard commercial grade unless otherwise stated.

Diethyl ether (ether) was dried by standing over anhydrous magnesium sulphate and then by distillation from sodium hydride. It was stored over sodium wire.

Petroleum ether refers to the fraction b.p. 50-70^{0}C. It was purified by distillation from phosphorus pentoxide and was stored over 4A^0 molecular sieves.

Ethyl acetate was purified by distillation from phosphorus pentoxide and was stored over 4A^0 molecular sieves.

EXPERIMENTAL RELATING TO CHAPTER 2.

3-Chloro-2,2-dimethylpropanoic acid (57)

A mixture of 2,2-dimethylpropanoic acid (56) (31g, 304 mmol), sulphuryl chloride (52.2ml, 619 mmol) and benzoyl peroxide (100mg, 0.4 mmol) in carbon tetrachloride (120ml) was heated at reflux under an ultraviolet light (Philips 240w sunlamp) for 3 h. The solution was concentrated under reduced pressure, then fractionally distilled through a spinning band column to give 2,2-dimethylpropanoic acid (56) (12g, 38%). Continued distillation gave 3-chloro-2,2-dimethylpropanoic acid (57) (20g, 48%):- b.p. 108-110°C/24 mm (lit.[41] 126-129°C/30 mm); ^{1}H n.m.r. (CCl_4) δ 1.31 (6H, s, 2xCH_3), 3.58 (2H, s, CH_2), 12.10 (1H, broad, OH).

N-*t*-Butyl-3-chloro-2,2-dimethylpropanamide (49).

A mixture of 3-chloro-2,2-dimethylpropanoic acid (57) (9g, 66 mmol), and thionyl chloride (5.4ml, 73 mmol), was heated under reflux for 3 h. The mixture was cooled, and petroleum ether (10ml) was added. The solution was dried ($MgSO_4$) and concentrated under reduced pressure. The residual oil was dissolved in dichloromethane (20ml), cooled in ice, and *t*-butylamine (11.6ml, 110 mmol) was added dropwise. After addition was complete, the solution was stirred at room temperature for 3 h, then dichloromethane (50ml) and water (50ml) were added. The dichloromethene layer was separated, then washed with

water (2x50ml). The combined aqueous solutions were extracted with dichloromethane (50ml). The dichloromethane solutions were combined, dried ($MgSO_4$), and concentrated under reduced pressure. The residue recrystallised from ethyl acetate-petroleum ether to give N-*t*-butyl-3-chloro-2,2-dimethylpropanamide (49) (2.3g, 18%):- m.p. 78-79°C (lit.[42] 76-77.5°C); ^1H n.m.r. (CCl_4) δ 1.20 (6H, s, 2 x CH_3), 1.32 (9H, s, $C(CH_3)_3$), 3.50 (2H, s, CH_2), 5.30 (1H, broad, NH).

1-*t*-Butyl-3,3-dimethylazetidin-2-one (42).

Sodium hydride (50% in oil, 1.1g, 46.7 mmol), prewashed with petroleum ether (2 x 10ml), was suspended in a mixture of dichloromethane and dimethylformamide (3:1, 100ml). To this suspension, a solution of N-*t*-butyl-3-chloro-2,2-dimethylpropanamide (49) (1.8g, 9.4 mmol) in dichloromethane and dimethylformamide (3:1, 20ml) was added dropwise. The solution was stirred at room temperature under nitrogen for 8 h, then water (10ml) was added and the resultant mixture was washed with water (3 x 50ml). The dichloromethane layer was dried ($MgSO_4$), and concentrated under reduced pressure. The residual oil was distilled to give 1-*t*-butyl-3,3-dimethylazetidin-2-one (42) (748mg, 51%):- b.p. 60-62°C/18mm (block); m/z 155.1308 (Calculated for $C_9H_{17}NO$ m/z 155.1310); υ_{max} (liquid film) 1740 cm^{-1}; ^1H n.m.r. (CCl_4) δ 1.21 (6H, s, 2 x CH_3), 1.30 (9H, s, $C(CH_3)_3$), 2.90 (2H, s, CH_2).

3-Hydroxy-2,2-dimethylpropanoic acid (59).

3-Hydroxy-2,2-dimethylpropanoic acid (59) was prepared as described by Testa and Co-workers.[43]

To a stirred solution of 2,2-dimethyl-1,3-propandiol (58) (Aldrich) (87g, 836 mmol) and sodium hydroxide (21.7g, 542 mmol) in water (1000ml), a solution of potassium permanganate (215g, 1.36 mmol) in water (3.5l) was added dropwise over 3½ h. The solution was left standing overnight at room temperature, then warmed until the pink colour faded. The solution was filtered and the solid residue was washed with water. The combined solutions were acidified with concentrated hydrochloric acid, then concentrated under reduced pressure. The crystalline residue was extracted with ether. The ether extracts were combined, dried ($MgSO_4$) and concentrated. The residue recrystallised from dichloromethane-petroleum ether to give 3-hydroxy-2,2-dimethylpropanoic acid (59) (41g, 41%):- m.p. 92-93°C (lit.[43] 120-123°C); ^1H n.m.r. (D_2O) δ 1.05 (6H, s, 2 x CH_3), 3.45 (2H, s, CH_2).

3-Bromo-2,2-dimethylpropanoic acid (60).

3-Bromo-2,2-dimethylpropanoic acid (60) was prepared as described by Greene and Hagermeyer [44].

A mixture of 3-hydroxy-2,2-dimethylpropanoic acid (59) (21g, 178 mmol) and 48% aqueous hydrobromic acid (213g) was heated under reflux for 20 h. The product was isolated by steam distillation of the reaction mixture and

extraction of the distillate with petroleum ether. The extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give a white crystaline solid, which recrystallised from ethyl acetate-petroleum ether to give 3-bromo-2,2-dimethylpropanoic acid (60) (25.5g, 79%):- m.p. 47-49°C (Lit.[44] 46-48°C); ^1H n.m.r. ($CDCl_3$) δ 1.33 (6H, s, 2 x CH_3), 3.50 (2H, s, CH_2), 12.17 (1H, broad, OH).

3-Bromo-2,2-dimethyl-N-phenylpropanamide (50).

A mixture of 3-bromo-2,2-dimethylpropanoic acid (60) (2g, 11 mmol), and thionyl chloride (1.6ml, 22 mmol) was heated under reflux for 3 h under nitrogen. The mixture was cooled and petroleum ether (10ml) was added. The solution was dried ($MgSO_4$) and concentrated under reduced pressure. The residual oil was dissolved in dichloromethane (50ml) and aniline (2.8ml, 31 mmol) was added dropwise. The solution was stirred for 4 h, then dichloromethane (50ml) and water (50ml) were added. The dichloromethane layer was separated, washed with water (2 x 50ml),, dried ($MgSO_4$)and concentrated under reduced pressure. The residue recrystallised from ethyl acetate-petroleum ether to give 3-bromo-2,2-dimethyl -N-phenylpropanamide (50) (1.5g, 53%):- m.p. 97-99°C; Found: C, 51.8; H, 5.4; N, 5.4% ($C_{11}H_{14}BrNO$ requires C, 51.6; H, 5.5; N, 5.4%); υ_{max} 1658 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 1.45 (6H, s, 2 x CH_3), 3.57 (2H, s, CH_2), 7.05 - 7.65 (6H, m, ArH and NH).

3,3-Dimethyl-1-phenylazetidin-2-one (43)

Sodium hydride (50% in oil, 345mg, 14 mmol) prewashed with petroleum ether (2 x 10ml) was suspended in a mixture of dichloromethane and dimethylformamide (4:1, 80ml). To this suspension a solution of 3-bromo-2,2-dimethyl-N -phenylpropanamide (50) (2.5g, 9.7 mmol) in dichloromethane and dimethylformamide (4:1, 20ml) was added dropwise over 30 min. The solution was stirred for 4 h under nitrogen, then a saturated solution of ammonium chloride (10ml) was added. The dichloromethane layer was separated, washed with a saturated solution of sodium chloride (5 x 50ml), dried ($MgSO_4$) and concentrated under reduced pressure. To remove the remaining dimethylformamide, the residual oil was dissolved in ether and dichloromethane (3:1, 150ml) then washed with saturated aqueous sodium chloride (3 x 50ml) and water (50ml). The dichloromethane layer was then dried ($MgSO_4$) and concentrated under reduced pressure. The resulting oil was distilled to give 3,3-dimethyl-1 -phenylazetidin-2-one (43) (1.1g, 64%):- b.p. 200-202°C/ 18mm (block); υ_{max} ($CDCl_3$) 1740 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 1.37 (6H, s, 2 x CH_3), 3.40 (2H, s, CH_2), 6.98 - 7.4 (5H, m, Ar-H). Spectral characteristics are consistent with those reported.[45]

N- *t*- Butyl-3-chloropropanamide (62).

t- Butylamine (6.1g, 83 mmol) was added dropwise to a solution of 3-chloropropanoyl chloride (61) (5g, 40 mmol) in dichloromethane (50ml). After stirring at room temperat-

ure for 3 h , dichloromethane (50ml) was added and the mixture was washed with water (3 x 30ml). The dichloromethane layer was dried ($MgSO_4$) and concentrated under reduced pressure to give a white crystalline residue which recrystallised from dichloromethane-petroleum ether to give N- *t*- butyl-3-chloropropanamide (62) (5.4g, 83%):- m.p. 78-80^{0}C; Found: C,51.6; H, 8.8; N 8.4% ($C_7H_{14}ClNO$ requires C, 51.4; H, 8.6; N, 8.5%); υ_{max} 1635 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 1.36 (9H, s, $C(CH_3)_3$), 2.53 (2H, t, J 6.5 Hz, CH_2CO), 3.76 (2H, t, J 6.5 Hz, CH_2Cl), 5.55 (1H, broad, NH).

Reaction of N- *t*-butyl-3-chloropropanamide (62) with sodium hydride.

N- *t*-Butyl-3-chloropropanamide (62) was treated with sodium hydride according to the method of Wasserman and co-workers.[28]

Sodium hydride (50% in oil, 400mg, 16.8 mmol), prewashed with petroleum ether (2 x 10ml), was suspended in a mixture of dichloromethane and dimethylformamide (4:1, 168ml). To this suspension a solution of N-*t*- butyl-3-chloropropanamide (62) (2.5g, 15.3 mmol) in dichloromethane and dimethylformamide (4:1, 168ml) was added dropwise over 3 h , under nitrogen. After stirring at room temperature for a further 3 h , a saturated solution of ammonium chloride (10ml) was added. The dichloromethane layer was separated, washed with saturated aqueous sodium chloride (5 x 100ml), dried ($MgSO_4$) and concentrated under

reduced pressure. The residual oil was dissolved in dichloromethane and ether (1:2, 150ml), then washed with saturated aqueous sodium chloride (5 x 100ml), dried ($MgSO_4$) and concentrated under reduced pressure. ^1H n.m.r. analysis of the residual oil showed no 1-*t*-butylazetidin-2-one (44) was present, as judged by comparison with the reported spectral characteristics of (44).[46]

Reaction of N-*t*-butyl-3-chloropropanamide (62) with potassium hydroxide under phase transfer conditions.

N-*t*-Butyl-3-chloropropanamide (62) was treated with potassium hydroxide in the presence of tetra-*n*-butyl -ammonium chloride according to the method of Takahata and co-workers.[29]

A solution of N-*t*-butyl-3-chloropropanamide (62) (815mg, 5 mmol) in tetrahydrofuran (100ml) was added dropwise over 6 h to a suspension of pulverised potassium hydroxide (336mg, 6 mmol) and tetra-*n*-butylammonium chloride (277mg, 1 mmol) in tetrahydrofuran (100ml). After stirring for a further 30 min the solution was filtered and the solid washed with dichloromethane. The combined filtrates were concentrated under reduced pressure. ^1H n.m.r. analysis of the residual oil showed no 1-*t*-butylazetidin-2-one (44) was present, as judged by comparison with the reported spectral characteristics of (44).[46]

1-*t*-Butylazetidin-2-one (44).

A solution of N-*t*-butyl-3-chloropropanamide (62) (2g, 12.2 mmol) and sodium iodide (5g, 33.3 mmol) in butan-2-one (20ml) was heated under reflux for 3 h , then cooled, and ether (150ml), was added. The resultant solution was filtered and the filtrate was concentrated under reduced pressure. The residue recrystallised from petroleum ether to give N-*t*-butyl-3-iodopropanamide (51):- ^{1}H n.m.r. ($CDCl_3$) δ 1.36 (9H, s, $C(CH_3)_3$), 2.68 (2H, t, J 6.5 Hz, CH_2CO), 3.35 (2H, t, J 6.5 Hz, CH_2I), 5.25 (1H, broad, NH).

Cyclisation of the crude iodide (51) was carried out according to the method of Wasserman and co-workers.[28]

Sodium hydride (50% in oil, 950mg, 39 mmol), pre-washed with petroleum ether (2 x 10ml), was suspended in a mixture of dichloromethane and dimethylformamide (4:1, 519ml). To this suspension a solution of the crude iodide (51) (2g, 7.9 mmol) in dichloromethane and dimethylformamide (4:1, 200ml) was added dropwise over 6 h , under nitrogen. The solution was stirred for a further 30 min then a saturated solution of ammonium chloride was added. The dichloromethane layer was separated, washed with saturated aqueous sodium chloride (5 x 100ml) and water (2 x 100ml), then dried ($MgSO_4$) and concentrated under reduced pressure. The residual oil was dissolved in ether and dichloromethane (3:1, 200ml). The resultant solution was washed with saturated aqueous sodium chloride (5 x 100ml) and water (2 x 100ml), dried ($MgSO_4$) and concentrated under reduced pressure. Petroleum ether (100ml) was added and the mixture

was cooled in an ice bath. The mixture was filtered and the filtrate was concentrated under reduced pressure to give an oil that was chromatographed on silica gel, gradient eluted with petroleum ether and ethyl acetate. The resulting oil was distilled to give 1-*t*-butylazetidin-2-one (44) (80mg, 5%):- b.p. 77-78°C/18mm (block); (lit.[55] 75°C/3.5mm); ^{1}H n.m.r. ($CDCl_3$) δ 1.36 (9H, s, $C(CH_3)_3$), 2.75 (2H, t, J 2.0 Hz, CH_2CO), 3.17 (2H, t, J 2.0 Hz, CH_2N).

3-Chloro-N-phenylpropanamide (52).

Aniline (7.7g, 83 mmol) was added dropwise to a solution of 3-chloropropanoyl chloride (61) (5g, 40 mmol) in dichloromethane (50ml). After stirring at room temperature for 3 h , dichloromethane (50ml) was added and the mixture was washed with water (3 x 50ml). The dichloromethane layer was dried ($MgSO_4$) and concentrated under reduced pressure to give 3-chloro-N-phenylpropanamide (52) (6.1g, 84%):- m.p. 115-116°C (lit.[47] 115-116.5°C); ^{1}H n.m.r. (acetone-d_6) δ 2.36 (2H, t, J 6.5 Hz CH_2CO), 3.40 (2H, t, J 6.5 Hz, CH_2CO), 6.3-7.3 (6H, m, ArH, NH).

1-Phenylazetidin-2-one (45).

Sodium hydride (50% in oil, 328mg, 13.6 mmol), prewashed with petroleum ether (2 x 10ml), was suspended in a mixture of dichloromethane and dimethylformamide (4:1, 400ml). To this suspension a solution of 3-chloro-N-phenylpropanamide (52) (1g, 5.5 mmol) in dichloromethane and dimethylformamide (4:1, 120ml) was

added dropwise over 6 h , under nitrogen. The solution was stirred for a further 30 min , then a saturated solution of ammonium chloride (10ml) was added. The dichloromethane layer was separated, dried ($MgSO_4$) and concentrated under reduced pressure to approximately 200ml. To this solution ether (200ml) was added and the mixture was washed with saturated aqueous sodium chloride (4 x 150ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residual oil was chromatographed on silica gel, gradient eluted with petroleum ether and ethyl acetate, to give 1-phenylazetidin-2-one (45) as white crystals (470mg, 58%):- m.p. 77-79^{0}C (lit.[48] 77-78^{0}C); ^{1}H n.m.r. ($CDCl_3$) δ 3.08 (2H, t, J 4.5 Hz, CH_2CO), 3.60 (2H, t, J 4.5 Hz, CH_2N), 7.26-7.36 (5H, m, Ar-H).

1-*t*-Butyl-3,3-diphenylazetidin-2-one (46).

A mixture of 3-chloro-2,2-diphenylpropanoic acid (64) [30] (1.8g, 7.0 mmol) and thionyl chloride (1.0ml, 14 mmol) was heated under reflux in dry apparatus for 3 h. The mixture was cooled and petroleum ether (10ml) was added. The solution was treated with $MgSO_4$, then filtered and concentrated under reduced pressure. The residual oil was dissolved in dichloromethane (50ml) and a solution of N-*t*-butylamine (1.9ml, 18 mmol) in dichloromethane (20ml) was added dropwise. After addition was complete the solution was stirred at room temperature for 9 h , then dichloromethane (50ml) and water (50ml) were added. The dichloromethane layer was separated, washed with water (2 x 50ml) then dilute hydrochloric acid (50ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residue recrystallised from ethyl acetate-petroleum

ether to give N-*t*-butyl-3-chloro-2,2-diphenylpropanamide (53) (600mg, 27%):- ^{1}H n.m.r. ($CDCl_3$) δ 1.25 (9H, s, $C(CH_3)_3$), 4.40 (2H, s, CH_2Cl), 5.52 (1H, broad, NH), 7.36 (10H, s, ArH).

Sodium hydride (50% in oil, 612mg, 25 mmol) prewashed with petroleum ether (2 x 10ml) was suspended in a mixture of dichloromethane and dimethylformamide (4:1, 80ml). To this suspension a solution of N-*t*-butyl-3-chloro-2,2 -diphenylpropanamide (53) (5.50mg, 1.7 mmol) in dichloro -methane and dimethylformamide (4:1, 20ml) was added dropwise. The solution was stirred at room temperature under nitrogen for 16 h , then a saturated solution of ammonium chloride (10ml) was added. The dichloromethane layer was separated, washed with a saturated solution of sodium chloride (3 x 100ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residue recrystallised from ethyl acetate-petroleum ether to give white crystalline 1-*t*-butyl-3,3 -diphenylazetidin-2-one (46), (325mg, 66%):- m.p. 149-150^{0}C; m/z 280.1620 (Calculated for $C_{19}H_{22}NO$ (M+1) m/z 280.1701 Found: C, 80.9; H, 7.6; N, 5.0% ($C_{19}H_{21}NO$ requires C, 81.6; H, 7.6; N, 5.0%); υ_{max} 1769 cm^{-1}; ^{1}H n.m.r. ($CDCl_3$) δ 1.36 (9H, s, $C(CH_3)_3$), 3.68 (2H, s, CH_2), 7.1-7.4 (10H, m, ArH).

3-Bromo-N,2,2-trimethylpropanamide (54)

A mixture of 3-bromo-2,2-dimethylpropanoic acid (60) (3.5g, 19 mmol) and thionyl chloride (2.78ml, 38 mmol) was heated under reflux in dry apparatus for 3 h. The solution was cooled and petroleum ether (10ml) was added. The solution was treated with $MgSO_4$, then filtered and concentrated under reduced pressure. The resulting oil

was dissolved in dichloromethane (75ml) and a 25% aqueous solution of methylamine (75ml) was added dropwise over 30 min. After addition was complete the solution was stirred at room temperature for 3 h , then dichloromethane (50ml) and water (50ml) were added. The dichloromethane layer was separated, washed with water (2 x 50ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residue recrystallised from dichloromethane-petroleum ether to give 3-bromo-N,2,2-trimethylpropanamide (54) (2.2g, 58%):- m.p. 57-58^{0}C; Found: C, 37.3; H, 6.4; N, 7.2% ($C_6H_{12}BrNO$ requires C, 37.1; H, 6.2; N, 7.2%); υ_{max} 1628 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 1.32 (6H, s, 2 x CH_3), 2.81 (3H, d, J 4 Hz, NCH_3), 3.50 (2H, s, CH_2Br), 6.22 (1H, broad, NH).

1,3,3-Trimethylazetidin-2-one (47).

Sodium hydride (50% in oil, 618mg, 26 mmol) pre-washed with petroleum ether (2 x 10ml) was suspended in a mixture of dichloromethane and dimethylformamide (4:1, 100ml). To this suspension a solution of 3-bromo-N,2,2-trimethyl -propanamide (54) (2g, 10 mmol) in dichloromethane and dimethylformamide (4:1, 40ml) was added dropwise. The solution was stirred at room temperature under nitrogen for 4 h , then a saturated solution of ammonium chloride (10ml) was added. The dichloromethane layer was separated, washed with a saturated solution of sodium chloride (3 x 100ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residual oil was chromatographed on a column of silica gel, gradient eluted with petroleum ether and ethyl acetate, to give an oil of 1,3,3-trimethylazetidin-2-one (47) (286mg, 24%):- b.p. 67-68^{0}C/18mm (block) (lit.[49]

71-72°C/20mm); ^{1}H n.m.r. ($CDCl_3$) δ 1.28 (6H, s, 2 x CH_3), 2.78 (3H, s, NCH_3), 3.03 (2H, s, CH_2).

N-Benzyl-3-bromo-2,2-dimethylpropanamide (55).

A mixture of 3-bromo-2,2-dimethylpropanoic acid (60) (3.7g, 20 mmol) and thionyl chloride (2.9ml, 40 mmol) was heated under reflux in dry apparatus for 3 h. The solution was cooled and petroleum ether (10ml) was added. The solution was treated with $MgSO_4$, then filtered and concentrated under reduced pressure. The resulting oil was dissolved in dichloromethane (50ml) and benzylamine (5.9ml, 54 mmol) was added dropwise. After addition was complete the solution was stirred at room temperature for 3 h , then dichloromethane (50ml) and water (50ml) were added. The dichloromethane layer was separated, washed with water (2 x 50ml) then dilute hydrochloric acid (50ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residual solid recrystallised from ethyl acetate-petroleum ether to give N-benzyl-3-bromo-2,2-dimethylpropanamide (55), (2.9g, 52%):- m.p. 50-51°C; Found: C, 53.6; H, 5.9; N, 5.1% ($C_{12}H_{16}BrNO$ requires C, 53.3; H, 5.9; N, 5.1%); υ_{max} 1628 cm^{-1}; ^{1}H n.m.r. ($CDCl_3$) δ 1.32 (6H, s, 2 x CH_3), 3.50 (2H, s, CH_2Br), 4.42 (2H, d, J 6 Hz, NCH_2), 6.15 (1H, broad, NH), 7.32 (5H, s, ArH).

1-Benzyl-3,3-dimethylazetidin-2-one (48).

Sodium hydride (50% in oil, 686mg, 26 mmol) pre-washed with petroleum ether (2 x 10ml) was suspended in a mixture of dichloromethane and dimethylformamide (4:1, 80ml). To this suspension a solution of N-benzyl-3-bromo -2,2-dimethylpropanamide (55) (2.9g, 10.7 mmol) in dichloromethane and dimethylformamide (4:1, 20ml) was added dropwise. The solution was stirred at room temperature under nitrogen for 4 h , then a saturated solution of ammonium chloride (25ml) was added. The dichloromethane layer was separated, washed with a saturated solution of sodium chloride (3 x 50ml), dried ($MgSO_4$) and concentrated under reduced pressure. The resulting oil was chromatographed on a column of silica gel, gradient eluted with petroleum ether and ethyl acetate, to give an oil of 1-benzyl-3,3-dimethylazetidin-2-one (48) (1.9g, 93%):- b.p. 130-132^{0}C/18mm (block); ^{1}H n.m.r. ($CDCl_3$) δ 1.25 (6H, s, 2 x CH_3), 2.85 (2H, s, CH_2), 4.27 (2H, s, CH_2Ph), 7.11-7.42 (5H, m, ArH). Spectral characteristics are in accord with those reported.[50, 51]

4-Benzoyloxy-1-*t*-butylazetidin-2-one (65).

A solution of 1-*t*-butylazetidin-2-one (44) (80mg, 0.63 mmol), *t*-butyl perbenzoate (0.44ml, 2 mmol) and cupric octanoate (10mg, 0.02 mmol) in benzene (5ml) was heated at reflux under nitrogen for 6 h. The solution was then washed with a saturated solution of sodium metabisulphite(3 x 25ml), dried ($MgSO_4$) and concentrated

under reduced pressure. The residue was chromatographed on silica gel, gradient eluted with petroleum ether and ethyl acetate, to give 4-benzoyloxy-1-*t*-butylazetidin-2-one (65) (92mg, 59%):- m.p. 94-95°C; m/z 247.1212 (Calculated for $C_{14}H_{17}NO_3$ m/z 247.1208); υ_{max} 1740, 1720 cm^{-1}, ^1H n.m.r. ($CDCl_3$) δ 1.40 (9H, s, $C(CH_3)_3$), 2.81 (1H, dd, J 1, 14 Hz, C3-H cis), 3.33 (1H, dd, J 4, 14 Hz, C3-H trans), 6.34 (1H, dd, J 1, 4 Hz, C4-H), 7.2-8.3 (5H, m, ArH).

4-Benzoyloxy-1-phenylazetidin-2-one (66).

Treatment of 1-phenylazetidin-2-one (45) (100mg, 0.68 mmol) with *t*-butyl perbenzoate (0.39ml, 2 mmol) in the presence of copper octanoate as described above for reaction of the azetidinone (44) with *t*-butyl perbenzoate, gave 4-benzoyloxy-1-phenylazetidin-2-one (66) (97mg, 53%):- m.p. 104-106°C; m/z 267.0895 (Calculated for $C_{16}H_{13}NO_3$ m/z 267.0870); Found: C, 72.2; H, 5.1; N, 4.6% ($C_{16}H_{13}NO_3$ requires: C, 71.9; H, 4.9; N, 5.2%) υ_{max} 1765, 1720 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 3.16 (1H, dd, J 2, 16 Hz, C3-H cis), 3.66 (1H, dd, J 4, 16 Hz, C3-H trans), 6.76 (1H, dd, J 2, 4 Hz, C4-H), 7.1-8.3 (10H, m, ArH).

4-Benzoyloxy-1-*t*-butyl-3,3-dimethylazetidin-2-one (67).

Treatment of 1-*t*-butyl-3,3-dimethylazetidin-2-one (42) (100mg, 0.65 mmol) with *t*-butyl perbenzoate (0.36ml, 2 mmol), in the presence of cupric octanoate, as described above for reaction of the azetidin-2-one (44) with *t*-butyl perbenzoate, gave 4-benzoyloxy-*t*-butyl-3,3-dimethylazetidin-2-one (67) (56mg, 27%):- m.p. 47-49°C;

Found: C, 69.7; H, 8.0; N, 4.8% ($C_{16}H_{21}NO_3$ requires C, 69.8; H, 7.6; N, 5.0%); υ_{max} (liquid film) 1760, 1720 cm^{-1}; ^1H n.m.r. (CCl_4) δ 1.10 (3H, s, CH_3), 1.34 (3H, s, CH_3), 1.39 (9H, s, $C(CH_3)_3$), 5.88 (1H, s, CH), 7.3-8.2 (5H, m, ArH).

4-Benzoyloxy-3,3-dimethyl-1-phenylazetidin-2-one (68).

Treatment of 3,3-dimethyl-1-phenylazetidin-2-one (43) (100mg, 0.57 mmol) with *t*-butyl perbenzoate (0.71ml, 3.7 mmol), in the presence of cupric octanoate, as described above for the reaction of the azetidinone (44) with *t*-butyl perbenzoate gave 4-benzoyloxy-3,3-dimethyl-1-phenylazetidin-2-one (68) (32mg, 19%):- b.p. 148-150°C/18mm (block); m/z 295.1208 (Calculated for $C_{18}H_{17}NO_3$ m/z 295.1212); υ_{max} 1770, 1720 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 1.34 (3H, s, CH_3), 1.53 (3H, s, CH_3), 6.42 (1H, s, CH), 7.1-8.3 (10H, m, ArH).

Treatment of 1-*t*-butyl-3,3-diphenylazetidin-2-one (46) with *t*-butyl perbenzoate.

Treatment of 1-*t*-butyl-3,3-diphenylazetidin-2-one (46) (100mg, 0.36 mmol) with *t*-butyl perbenzoate (0.39ml, 1.07 mmol), in the presence of copper octanoate, as described above for reaction of the azetidin-2-one (44) with *t*-butyl perbenzoate afforded only starting material (46) (93%). There was no evidence for benzoyloxylation as judged by ^1H n.m.r. analysis.

Reaction of 1,3,3-trimethylazetidin-2-one (47) with *t*-butyl perbenzoate.

Treatment of 1,3,3-trimethylazetidin-2-one (47) (100mg, 0.9 mmol) with *t*-butyl perbenzoate (1.5ml, 8 mmol) in the presence of cupric octanoate as described above for reaction of the azetidin-2-one (44) with *t*-butyl perbenzoate gave an oil consisting of 3 components. Preparative HPLC gave 4-benzoyloxy-1-benzoyloxymethyl-3,3-dimethylazetidin-2-one (71) and a mixture of 4-benzoyloxy-1,3,3-dimethylazetidin-2-one (69) and 1-benzoyloxymethyl-3,3-dimethylazetidin-2-one (70). The benzoyloxyazetidin-2-ones (69) and (70) were inseparable by chromatography on a chromatotron silica gel place or by HPLC. Analysis of reaction mixtures after short reaction times showed that the mono-substituted azetidin-2-ones (69) and (70) were the primary products of reaction produced in the ratio ca. 1:2. The disubstituted azetidin-2-one (71) was a secondary product, produced by further reaction of (69) and (70). 4-Benzoyloxy-1-benzoyloxymethyl-3,3-dimethylazetidin-2-one (71):- m/z 353.1246 (Calculated for $C_{20}H_{19}NO_5$ m/z 353.1263); υ_{max} 1784, 1716 cm^{-1}; ^1H n.m.r. (XL-300) ($CDCl_3$) δ 1.31 (3H, s, CH_3), 1.45 (3H, s, CH_3), 5.58 (2H, s, NCH_2), 6.13 (1H, s, CH), 7.3-8.3 (10H, m, ArH).

4-Benzoyloxy-1,3,3-trimethylazetidin-2-one (69) and 1-benzoyloxymethyl-3,3-dimethylazetidin-2-one (70):- m/z 233.1060 (Calculated for $C_{13}H_{15}NO_3$ m/z 233.1052); υ_{max} (liquid film) 1772, 1722 cm^{-1};For (69): ^1H n.m.r. ($CDCl_3$) δ 1.33 (3H, s, CH_3), 1.40 (3H, s, CH_3), 2.91 (3H, s, NCH_3), 5.88 (1H, s, CH), 7.3-8.3 (5H, m, ArH); For (70): ^1H n.m.r. ($CDCl_3$) δ 1.33 (6H, s, 2 x CH_3), 3.32 (2H, s, CH_2), 5.45

(2H, s, NCH_2O), 7.3-8.3 (5H, m, ArH).

Reaction of 1-benzyl-3,3-dimethylazetidin-2-one (48) with *t*-butyl perbenzoate.

Treatment of 1-benzyl-3,3-dimethylazetidin-2-one (48) (100mg, 0.52 mmol) with *t*-butyl perbenzoate (0.30ml, 1.6 mmol) in the presence of cupric octanoate as described above for reaction of the azetidin-2-one (44) with *t*-butyl perbenzoate gave 3,3-dimethyl-1-(α-hydroxybenzyl)azetidin-2-one (73) (13.7mg, 12%):- m.p. 83-85°C; m/z 203.0950 (Calculated for $C_{12}H_{13}NO_2$ (M^+-2) 203.0947); υ_{max} ($CDCl_3$) 1740 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 1.26 (3H, s, CH_3), 1.33 (3H, s, CH_3), 2.68 (1H, d, J 6 Hz, CH), 3.14 (1H, d, J 6 Hz, CH), 4.30 (1H, broad, OH), 6.36 (1H, s, CH), 7.2-7.6 (5H, m, ArH).

EXPERIMENTAL RELATING TO CHAPTER 3

N-*t*-Butyl-4-chlorobutanamide (75).

A solution of *t*-butylamine (18.7ml, 177 mmol) in dichloromethane (30ml) was added dropwise to a solution of 4-chlorobutanoyl chloride (74) (7.9ml, 71 mmol) in dichloromethane (20ml). After stirring at room temperature for 4 h , dichloromethane (50ml) was added and the mixture was washed with water (3 x 30ml). The dichloromethane layer was dried ($MgSO_4$) and concentrated under reduced pressure to give white crystalline material which recrystallised from petroleum ether to give N-*t*-butyl-4-chlorobutanamide (75) (10.4g, 82%):- m.p. 46- 48^{0}C; Found: C, 54.1; H, 9.1; N, 7.8% ($C_8H_{16}ClNO$ requires C, 54.1; H, 9.1; N, 7.8%) υ_{max} 1648 cm^{-1}; ^1H n.m.r. δ 1.33 (9H, s, $C(CH_3)_3$), 2.13 (4H, m, $COCH_2CH_2$),3.93 (2H, t, J 6Hz, CH_2Cl), 5.33 (1H, broad, NH).

1-*t*-Butylpyrrolidin-2-one (76)

Sodium hydride (50% in oil, 850mg, 38 mmol) prewashed with petroleum ether (2 x 10ml) was suspended in a mixture of dichloromethane and dimethylformamide (4:1, 40ml). To this suspension a solution of N-*t*-butyl-4-chlorobutanamide (75) (2.5g, 14 mmol) in dichloromethane and dimethylformamide (4:1, 30ml) was added dropwise. The solution was stirred at room temperature, under nitrogen for 4 h , then a saturated solution of ammonium chloride (10ml) was added. The

dichloromethane layer was separated and added to ether (100ml). The solution was washed with a saturated solution of sodium chloride (5 x 100ml) then water (100ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residual oil was dissolved in ether and dichloromethane (3:1, 200ml) and washed with a saturated solution of sodium chloride (5 x 100ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residual oil was distilled to afford 1-*t*-butylpyrrolidin-2-one (76) (1.5g, 75%) b.p. 65-67^{0}C/18mm (block); m/z 141.1151 (Calculated for $C_8H_{15}NO$ m/z 141.1153); υ_{max} 1674 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 1.35 (9H, s, $C(CH_3)_3$), 2.08 (4H, m, $COCH_2CH_2$), 3.88 (2H, t, J 3.5Hz, CH_2N).

4-Chloro-N-phenylbutanamide (77).

A solution of aniline (16.3ml, 177 mmol) in dichloromethane (30ml) was added dropwise to a solution of 4-chlorobutanoyl chloride (74) (79.3ml, 79.2 mmol) in dichloromethane (20ml). After stirring at room temperature for 4 h , dichloromethane (50ml) was added and the mixture washed with water (3 x 50ml). The dichloromethane layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residual material recrystallised from dichloromethane-petroleum ether. To remove the remaining pyridine salts the crystalline material was dissolved in dichloromethane (50ml), then washed with dilute hydrochloric acid (50ml), dried ($MgSO_4$) and concentrated under reduced pressure. Recrystallisation from dichloromethane-petroleum ether gave 4-chloro-N-phenylbutanamide (77) (6.6g, 47%):- m.p. 68.5-70.5^{0}C, (lit.[47] 70-71^{0}C); ^1H n.m.r. ($CDCl_3$) δ 2.23 (2H, t, J 2.5Hz, CH_2), 2.25 (2H, t, J 2.5Hz, CH_2), 3.63

(2H, t, J 3Hz, CH_2Cl), 7.26-8.2 (5H, m, ArH).

1-Phenylpyrrolidin-2-one (78).

Sodium hydride (50% in oil, 713mg, 32 mmol) prewashed with petroleum ether (2 x 10ml) was suspended in a mixture of dichloromethane and dimethylformamide (4:1, 40ml). To this suspension a solution of 4-chloro-N-phenylbutanamide (77) (2.5g, 12 mmol) in dichloromethane and dimethylformamide (4:1, 30ml) was added dropwise. The suspension was stirred at room temperature under nitrogen for 4 h , then a saturated solution of ammonium chloride (10ml) was added. The dichloromethane layer was separated and added to ether (100ml). The solution was washed with a saturated solution of sodium chloride (5 x 100ml), then the dichloromethane layer was added to ether (100ml). The solution was washed with saturated solution of sodium chloride (5 x 100ml) then water (100ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residual material recrystallised from dichloromethane-petroleum ether to afford 1-phenylpyrrolidin-2-one (78) (1.8g, 87%): m.p. 60-62^{0}C, (lit.[52] 67-68^{0}C); ^{1}H n.m.r. ($CDCl_3$) δ 2.43 (4H, m, $COCH_2CH_2$), 3.88 (2H, t, J 3.5Hz, CH_2N), 7.42 (5H, m, ArH). Spectral characteristics are in accord with those reported.[52]

1,3,3-Trimethylpyrrolidin-2-one (80).

1,3,3-Trimethylpyrrolidin-2-one (80) was prepared according to the method of Gassman and Fox.[34]

To a suspension of sodium amide prepared from

sodium (10.2g, 443 mmol) and ferric nitrate (30mg, 0.09 mmol) in ammonia (500ml), 1-methylpyrrolidin-2-one (79) (19.2g, 193 mmol) was added dropwise over 30 min. The suspension was stirred for 20 min, then methyl iodide (56.8g, 400 mmol) was added dropwise over 1 hr. The suspension was left stirring for a further 1 h , then ether (150ml) was added and the suspension was allowed to warm to room temperature overnight. Ether (150ml) was then added and decanted. A 95% ethanol solution (200ml) was added followed by water (100ml). The aqueous solution was extracted with ether (6 x 500ml), the ether extracts were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The residual oil was distilled using a spinning band column to give 1,3,3-trimethylpyrrolidin-2-one (80) (1.7g, 6.9%):- b.p. 65-70^{0}C/13mm (lit.[34] 72-73^{0}C/20mm); ^{1}H n.m.r. (CCl_4) δ 1.02 (6H, s, 2 x CH_3), 1.78 (2H, t, J 6.5Hz, CH_2), 2.72 (3H, s, NCH_3), 3.22 (2H, t, J 6.5Hz, CH_2). Other fractions of varying purity were also obtained. Spectral properties are consistent with those reported.[34]

Treatment of 1-*t*-butylpyrrolidin-2-one (76) with *t*-butylperbenzoate.

Treatment of 1-*t*-butylpyrrolidin-2-one (76) (540mg, 3.8 mmol) with *t*-butyl perbenzoate (0.73ml, 3.8 mmol) in the presence of cupric octanoate, as described above for reaction of the azetidin-2-one (44) with *t*-butyl perbenzoate, afforded none of the C5-benzoyloxylated material (82) as judged by ^{1}H n.m.r. analysis. Signals were observed at δ 6.13 (1H, d, J 6Hz), 6.83 (d, J 2Hz), and 7.03 (1H, dd, J 2,6Hz).

Treatment of 1-phenylpyrrolidin-2-one (78) with *t*-butyl perbenzoate.

Treatment of 1-phenylpyrrolidin-2-one (78) (125mg, 0.78 mmol) with *t*-butyl perbenzoate (0.148ml, 0.78 mmol) in the presence of cupric octanoate as described above for reaction of the azetidin-2-one (44) with *t*-butyl perbenzoate afforded none of the C5-benzoyloxylated material as judged by ^{1}H n.m.r. analysis.

1-Hydroxymethyl-3,3-dimethylpyrrolidin-2-one (87) and 5-hydroxy-1,3,3-trimethylpyrrolidin-2-one (90).

Treatment of 1,3,3-trimethylpyrrolidin-2-one (80) (158mg, 1.24 mmol) with *t*-butyl perbenzoate (0.236ml, 1.24 mmol) in the presence of cupric octanoate for 4 h , as described above for reaction of the azetidin-2-one (44) with *t*-butyl perbenzoate, gave 1-hydroxymethyl-3,3-dimethylpyrrolidin-2-one (87) and 5-hydroxy-1,3,3-trimethylpyrrolidin-2-one (90). The pyrrolidin-2-ones (87) and (90) were produced through hydrolysis of the corresponding benzoates (86) and (89) during chromatography. Analysis of reaction mixtures after 2 h showed the ratio of (86) to (89) to be ca. 1:4. 1-Hydroxymethyl-3,3-dimethylpyrrolidin-2-one (87) (50mg, 28%):- b.p. 78-80^{0}C/18mm (block); m/z 143.0944 (Calculated for $C_7H_{13}NO_2$ m/z 143.0946); υ_{max} (liquid film), 1695 cm^{-1}; ^{1}H n.m.r. ($CDCl_3$) δ 1.15 (3H, s, CH_3), 1.16 (3H, s, CH_3), 1.93 (2H, m, CH_2), 3.45 (2H, m, CH_2), 4.75 (2H, d, J 5Hz, NCH_2O), 6.83 (1H, broad, OH). 5-Hydroxy-1,3,3-trimethylpyrrolidin-2-one (90) (30mg, 16%):- b.p. 102-110^{0}C/18mm

(block); m/z 143.0943 (Calculated for $C_7H_{13}NO_2$ 143.0946); υ_{max} (liquid film) 3200, 1680 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 1.08 (3H, s, CH_3), 2.21 (3H, s, CH_3), 1.93 (2H, m, CH_2), 2.78 (3H, s, NCH_3), 5.0 (1H, broad, OH), 5.05 (1H, dd, J 4, 7Hz, CH).

EXPERIMENTAL RELATING TO CHAPTER 4

N-Benzoylvaline methyl ester (19).

Thionyl chloride (18.3ml, 256 mmol) was added dropwise to methanol (150ml). Then D,L-valine (91) (10.6g, 85 mmol) was added and the solution was stirred at room temperature in dry apparatus for 3 h. The solution was concentrated under reduced pressure to give crude valine methyl ester hydrochloride (92).

Benzoyl chloride (14.7ml, 128 mmol) was added dropwise to a mixture of the crude valine methyl ester (92) in water (100m) and ethyl acetate (100ml). The solution was kept basic by adding potassium bicarbonate as required. The solution was stirred at room temperature overnight then the aqueous layer was separated and extracted with ethyl acetate (2 x 50ml). The ethyl acetate solutions were combined, washed with a 5% aqueous solution of potassium bicarbonate, dried ($MgSO_4$) and concentrated under reduced pressure. The residue recrystallised from ethyl acetate-petroleum ether to give N-benzoylvaline methyl ester (19) (5.6g, 26%):- m.p. 109-110.5^{0}C (lit.[37,53] 110.5-111^{0}C); ^{1}H n.m.r. ($CDCl_3$) δ 1.00 (6H, d, J 6.5Hz, 2 x CH_3), 2.27 (1H, m, CH), 3.73 (3H, s, OCH_3), 4.75 (1H, dd, J 4,9Hz,CH), 6.62, (1H, broad, NH), 7.2-8.0 (5H, m, ArH).

Methyl 3-bromo-3-methyl-2-oxobutanoate (97).

A solution of N-benzoylvaline methyl ester (19) (1g, 4.3 mmol), NBS (1.8g, 10.1 mmol) and benzoylperoxide

(50mg, 0.2 mmol) in carbon tetrachloride (20ml) was heated at reflux, under nitrogen for 1 h. The cooled solution was filtered then concentrated under reduced pressure. The residual oil was chromatographed on a column of silica gel. Elution with a gradient of petroleum ether and ethyl acetate gave methyl 3-bromo-3-methyl-2-oxobutanoate (97) (710mg, 79%):- m/z 210, 208 (M+); υ_{max} 1740, 1720 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 1.98 (6H, s, 2 x CH_3), 3.90 (3H, s, OCH_3).

Methyl 2-benzamido-3-methylbutenoate (98).

A mixture of N-benzoylvaline methyl ester (19) (504mg, 2.1 mmol), NBS (1.17mg, 6.6 mmol) and benzoylperoxide (5mg, 0.02 mmol) in carbon tetrachloride (30ml) was heated at reflux under nitrogen for 35 min. The cooled solution was filtered and concentrated under reduced pressure to give a yellow oil of N-benzoyl-2,3-dibromovaline methyl ester (41):- ^1H n.m.r. ($CDCl_3$) δ 2.18 (6H, s, 2 x CH_3), 3.17 (3H, s, OCH_3), 7.33-8.03 (5H, m, ArH).

A sample of N-benzoyl-2,3-dibromovaline methyl ester (41) (100mg, 0.255 mmol) in pyridine (3ml) was heated at reflux under nitrogen for 35 min. Chloroform (25ml) was added and the solution washed with dilute hydrochloric acid (3 x 50ml), then water (2 x 50ml), dried ($MgSO_4$), and concentrated under reduced pressure. The residue recrystallized from ethyl acetate-petroleum ether to give methyl 2-benzamido-3-methylbutenoate (98) (25mg, 25%):- m.p. 125-128°C (lit.[54] 124-125°).

N-Benzoyl-3-bromovaline methyl ester (93).

A solution of N-benzoyl-2,3-dibromovaline methyl ester (41) (110mg, 0.28 mmol) and tri-*n*-butyltin hydride (Aldrich, 81mg, 0.28 mmol) in benzene (1ml) was left standing at room temperature under nitrogen for 35 min. The solution was concentrated under reduced pressure then chromatographed on a column of silica gel gradient eluted with petroleum ether and ethyl acetate, to give an oil containing a mixture of N-benzoyl-3-bromovaline methyl ester (93) and N-benzoylvaline methyl ester (41). HPLC analysis of the reaction mixture showed that (93) and (19) were formed in the ratio ca. 7.7:1. N-Benzoyl-3-bromovaline methyl ester (93) was separated by preparative HPLC (22mg, 25%):- m.p. 50-52°C; m/z 315.0279 (Calculated for $C_{13}H_{16}BrNO_3$ 315.0294); υ_{max} 1747, 1650 cm^{-1}; ^1H n.m.r. (CCl_4) δ 1.83 (3H, s, CH_3), 2.02 (3H, s, CH_3), 3.80 (3H, s, OCH_3), 4.78 (1H, dd, J 5,9Hz, CH), 6.85 (1H, broad, NH), 7.2-7.8 (5H, m, ArH).

EXPERIMENTAL RELATING TO CHAPTER 5.

N-(3-Bromo-2,2-dimethylpropanoyl)valine methyl ester (100).

Thionyl chloride (9.4ml, 129 mmol) was added dropwise to methanol (150ml). The, D,L-valine (91) (7.6g, 65 mmol) was added and the solution was stirred at room temperature in dry apparatus for 3 h. The solution was then concentrated under reduced pressure to give crude valine methyl ester hydrochloride (92).

A solution of 3-bromo-2,2-dimethylpropanoic acid (60) (7.8g, 43 mmol) and thionyl chloride (6.3ml, 86 mmol) was heated under reflux in dry apparatus for 3 h. After cooling petroleum ether (10ml) was added, the solution was treated with $MgSO_4$, filtered and concentrated under reduced pressure. The residual oil was dissolved in dichloromethane (100ml) and a solution of the crude valine methyl ester (92) in dichloromethane (50ml) and water (50ml) was added. Potassium bicarbonate was added as required to keep the solution basic. The mixture was stirred for 4 h , then the dichloromethane layer was separated, washed with water (3 x 50ml), dried ($MgSO_4$), and concentrated under reduced pressure to give white crystalline material which recrystallised from petroleum ether to give N-(3-bromo-2,2-dimethylpropanoyl)valine methyl ester (100) (6.2g, 32%):- m.p. 55-56^{0}C; Found: C, 45.0; H, 6.9; N, 4.7% ($C_{11}H_{20}BrNO_3$ requires C, 45.0; H, 6.9; N, 4.7%) υ_{max} 1750, 1632 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 0.92 (3H, d, J 6Hz, CH_3), 0.95 (3H, d, J 6Hz, CH_3), 1.35 (6H, s, 2 x CH_3), 2.15 (1H, m, CH), 3.50 (2H, d, J 2Hz, CH_2), 3.75 (3H, s, OCH_3), 4.56 (1H, dd, J 4, 13Hz, NCH), 6.2 (1H, broad, NH).

N-(3-Chloro-2,2-dimethylpropanoyl)valine methyl ester (109).

Thionyl chloride (18.3ml,256 mmol) was added dropwise to methanol (150ml). The, D,L-valine (91) (10g, 85 mmol) was added and the solution was stirred at room temperature in dry apparatus for 3 h. The solution was then concentrated under reduced pressure to give crude valine methyl ester hydrochloride (92).

A solution of 3- chloro-2,2-dimethylpropanoic acid (57) (10.4g,76 mmol) and thionyl chloride (11ml, 152 mmol) was heated under reflux in dry apparatus for 3 h. After cooling petroleum ether (10ml) was added, the solution was treated with $MgSO_4$, filtered and concentrated under reduced pressure. The residual oil was dissolved in dichloromethane (100ml) and a solution of the crude valine methyl ester (92) in dichloromethane (50ml) and water (50ml) was added. Potassium bicarbonate was added as required to keep the solution basic. The mixture was stirred for 4 h , then the dichloromethane layer was separated, washed with water (3 x 50ml), dried ($MgSO_4$), and concentrated under reduced pressure to give white crystalline material which recrystallised from petroleum ether to give N-(3-chloro-2,2-dimethylpropanoyl-valine methyl ester (109) (3.1g, 14%):- m.p. 62-63^{0}C; υ_{max} 1760, 1630 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 0.70 (3H, d, J 2Hz, CH_3), 0.98 (3H, d, J 2Hz, CH_3), 1.33 (6H, s, 2 x CH_3) 2.16 (1H, m, CH), 3.61 (2H, d, J 2Hz, CH_2), 3.75 (3H, s, OCH_3), 4.55 (1H, dd, J 4, 13Hz, NCH), 6.26 (1H, broad, NH).

1-(1-Methoxycarbonyl-2-methylpropyl)-3,3-dimethylazetidin-2-one (31).

Sodium hydride (50% in oil, 383mg, 16 mmol) pre-washed with petroleum ether (2 x 10ml) was suspended in a mixture of dichloromethane and dimethylformamide (3:1, 80ml). To this suspension a solution of N-(3-chloro-2,2-dimethylpropanoyl)valine methyl ester (109) (1.26g, 5.1 mmol) in dichloromethane and dimethylformamide (3:1, 20ml) was added dropwise. The solution was stirred for 6 h , under nitrogen, then water (10ml) was added. The dichloromethane layer was separated, washed with water (3 x 50ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residual oil was distilled to give 1-(1-methoxycarbonyl-2-methylpropyl)-3,3-dimethylazetidin-2-one (31),(.39g, 36%):- b.p. 150-152°C /18mm (block); m/z 213.1361 (Calculated for $C_{11}H_{19}NO_3$ m/z 213.1364); υ_{max} 1740, 1722 cm^{-1}; ^1H n.m.r. (CCl_4) δ 0.92 (3H, s, CH_3), 1.03 (3H, s, CH_3), 1.28 (6H, s, 2 x CH_3), 2.15 (1H, m, CH), 3.10 (1H, d, J 6Hz, CH), 3.31 (1H, d, J 6Hz, CH), 3.73 (3H, s, OCH_3), 4.06 (1H, d, J 8Hz, CH).

Treatment of 1-(1-Methoxycarbonyl-2-methylpropyl)-3,3-dimethylazetidin-2-one (31) with *t*-butyl perbenzoate.

Treatment of 1-(1-Methoxycarbonyl-2-methylpropyl)-3,3-dimethylazetidin-2-one (31) (200mg, 0.9 mmol) with *t*-butyl perbenzoate (1.06ml, 5.6 mmol) in the presence of cupric octanoate as described above for the reaction of the azetidin-2-one (44) with *t*-butyl perbenzoate gave only start-

ing material (31) (189mg, 95%).

Treatment of 1-(1-Methoxycarbonyl-2-methylpropyl)-3,3 -dimethylazetidin-2-one (31) with NBS.

A mixture of 1-(1-Methoxycarbonyl-2-methylpropyl) -3,3-dimethylazetidin-2-one (31) (500mg, 2.3 mmol) NBS (2.09g, 11.7 mmol) and benzoyl peroxide (5mg, 0.02 mmol) in carbon tetrachloride (20ml) was heated at reflux under nitrogen for 2 h. The cooled solution was filtered and concentrated under reduced pressure. ^{1}H n.m.r. analysis of the residual oil indicated extensive decomposition and formation of methyl 3-bromo-3-methyl-2-oxobutanoate (97). No 1-(2,3-dibromo-1-methoxycarbonyl-2-methylpropyl)-3,3 -dimethylazetidin-2-one (101) was detected.

Treatment of 1-(1-methoxycarbonyl-2-methylpropyl)-3,3 -dimethylazetidin-2-one(31) with sulphuryl chloride.

A mixture of 1-(1-methoxycarbonyl-2-methylpropyl)-3,3 -dimethylazetidin-2-one (31) (200mg, 0.9 mmol), sulphuryl chloride (0.23ml, 2.8 mmol) and benzoyl peroxide (10mg, 0.04 mmol) in benzene (5ml) was heated at reflux in dry apparatus for 15 min. The solution was cooled, filtered and concentrated under reduced pressure. The residual oil was chromatographed on a chromatotron silica gel plate, gradient eluted with petroleum ether and ethyl acetate. ^{1}H n.m.r. and HPLC analysis of several fractions from the

plate indicated the presence of 1-(2-chloro-1-methoxycarbonyl -2-methylpropyl)-3,3-dimethylazetidin-2-one (102) (see below).

1-(1-Methoxycarbonyl-2-methylprop-1-enyl)-3,3-dimethylazetidin -2-one (104).

A solution of N-(3-bromo-2,2-dimethylpropanoyl)valine methyl ester (100) (6.1g, 20.7 mmol), sulphuryl chloride (10.7ml, 116 mmol) and benzoyl peroxide (100mg, 0.4 mmol) in benzene (20ml), was heated under reflux in dry apparatus for 8 h. The solution was cooled, then concentrated under reduced pressure. The resulting oil was chromatographed on a column of silica gel to give a yellow oil of N-(3-bromo-2,2 -dimethylpropanoyl)-3-chlorovaline methyl ester (103) and unreacted starting material (100).

Sodium hydride (50% in oil, 740mg, 30.8 mmol) pre-washed with petroleum ether (2 x 10ml) was suspended in a mixture of dichloromethane and dimethylformamide (4:1, 100ml). To this suspension a solution of crude N-(3-bromo-2,2 -dimethylpropanoyl)-3-chlorovaline methyl ester (103) (3.0g, 10.3 mmol) in dichloromethane and dimethylformamide (4:1, 20ml) was added dropwise. This solution was stirred at room temperature for 4 h , under nitrogen, then a saturated solution of ammonium chloride (10ml) was added. The dichloromethane layer was separated and added to ether (200ml). This solution was washed with a saturated solution of sodium chloride (6 x 150ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residual oil was chromatographed on silica gel, gradient eluted with petroleum ether and

ethyl acetate, to give 1-(1-methoxycarbonyl-2-methylpropyl) -3,3-dimethylazetidin-2-one (31) (110mg 2.4%) and 1-(1-methoxycarbonyl-2-methylprop-1-enyl)-3,3-dimethylazetidin -2-one (104) (259mg, 5.9%):- b.p. 96-98°C/16mm (block); m/z 211.1208 (Calculated for $C_{11}H_{19}NO_3$ m/z 211.1208); υ_{max} (liquid film) 1758, 1720 cm^{-1}; ^1H n.m.r. (CCl_4) δ 1.30 (6H, s, 2 x CH_3), 1.88 (3H, s, CH_3), 2.17 (3H, s, CH_3), 3.19 (2H, s, CH_2), 3.73 (3H, s, OCH_3). Other fractions containing varying proportions of both (104) and (31) (totalling 1.2g) were also isolated.

1-(2-Chloro-1-methoxycarbonyl-2-methylpropyl)-3,3 -dimethylazetidin-2-one (102).

A mixture of 1-(1-methoxycarbonyl-2-methylprop-1-enyl) -3,3-dimethylazetidin-2-one (104) (100mg, 0.474 mmol) and sulphuryl chloride (200mg, 1.5 mmol) in carbon tetrachloride (2ml) was stirred at room temperature under nitrogen for 15 min then concentrated under reduced pressure.

The resulting oil was dissolved in benzene (2ml), then tri-*n*-butyltin hydride (Aldrich, 0.38ml, 1.4 mmol) was added. This solution was stirred for 2 h under nitrogen then concentrated under reduced pressure. The oily residue was chromatographed on silica gel, gradient eluted with petroleum ether and ethyl acetate, to give 1-(1-methoxycarbonyl -2-methylpropyl)-3,3-dimethylazetidin-2-one (31) and 1-(2-chloro-1-methoxycarbonyl-2-methylpropyl)-3,3-dimethyl- azetidin-2-one (102):- m/z 247.0970 (Calculated for

$C_{11}H_{18}ClNO_3$ m/z 247.0975); υ_{max} 1755, 1740 cm^{-1}; ^1H n.m.r. (XL-300) ($CDCl_3$) δ 1.32 (3H, s, CH_3), 1.35 (3H, s, CH_3), 1.68 (3H, s, CH_3), 1.75 (3H, s, CH_3), 3.50 (1H, d, J 1Hz, CH), 3.63 (1H, d, J 1Hz, CH), 3.78 (3H, s, OCH_3), 4.61 (1H, s, CH).

REFERENCES

1. FLEMING, A., *Brit. J. Exp. Path.*, 1929, 10, 226.

2. CHAIN, E., FLOREY, H.W., GARDNER, A.D., JENNINGS, M.A., ORR-EWING, T., SANDERS, A.F., and HEATLEY, N.G. *Lancet*, 1940, 2, 226.

3. *'The Chemistry of Penicillin'*, CLARKE, H.T., JOHNSON, J.R., and ROBINSON, R., (Princeton University Press : New Jersey, 1949)

4. SHEEHAN, J.C., and HENERY-LOGAN, K.R., *J. Am. Chem. Soc.*, 1957, 79, 1262; 1959, 81, 3089.

5. *'Ullmann's Encyclopedia of Industrial Chemistry'*, (Edited by Gerhartz, W.), Vol A2, p.p. 469-484, (Weinheim, 1985).

6. ARNSTEIN, H.R.V., and MORRIS, D., *Biochem. J.*, 1960, 76,323.

7. ABRAHAM, E.P., and LODER, P.B., *Biochem, J.*, 123, 471.

8. ABERHART, D.J., *Tetrahedron*, 1977, 33 , 1545.

9. BAXTER, R.L., THOMSON, G.A., and SCOTT, A.I., *J. Chem. Soc., Chem. Commun.*, 1984, 32.

10. BALDWIN, J.E., ABRAHAM, E.P., ADLINGTON, R.M., CRIMMIN, M.J., FIELD, L.D., JAYATILAKE, G.S., WHITE, R.L. and USHER, J.J., *Tetrahedron*, 1984, 40, 1907.

11. MEESSCHAERT, B., ADRIAENS, P., and EYSSEN, H., *J. Antibiotics.*, 1980, 33, 722

12. BALDWIN, J.E., ADLINGTON, R.M., MORONEY, S.E., FIELD, L.D., and TING, H.H., *J. Chem. Soc., Chem. Commun.*, 1984, 984; BALDWIN, J.E., ADLINGTON, R.M., and BOHLMAN, R., *J. Chem. Soc., Chem. Commun.*, 1985, 357.

13. BALDWIN, J.E. and DAVIS, A.P., *J. Chem. Soc., Chem. Commun.*, 1981, 1219.

14. EASTON, C.J., *J. Chem. Soc., Chem. Commun*, 1983, 1349; EASTON, C.J., *J. Chem. Soc., Perkin Trans. I.*, 1985, 153.

15. BALDWIN, J.E., DAVIES, A.P., and FIELD, L.D., *Tetrahedron*, 1982, 38, 2777.

16. BECKWITH, A.L.J., and EASTON, C.J., *Tetrahedron*, 1983, 39, 3995.

17. NALLY, J., ORDSMITH, N.H.R., and PROCTER, G., *Tetrahedron. Lett*, 1985, 26, 4107.

18. BALDWIN, J.E., BECKWITH, A.L.J., DAVIS, A.P., PROCTER, G., and SINGLETON, K.E., *Tetrahedron*, 1981, 37, 2181.

19. ADLINGTON, R.M., APLIN, R.T., BALDWIN, J.E., CHAKRAVARTI, B., FIELD, L.D., JOHN, E.M., ABRAHAM, E.P., and WHITE, R.L., *Tetrahedron*, 1983, 39, 1061.

20. BALDWIN, J.E., and WAN, T.S., *J. Chem. Soc., Chem. Commun.*, 1979, 249.

21. EASTON, C.J., and BOWMAN, N.J., *J. Chem. Soc., Chem. Commun.*, 1983, 1193.

22. BALDWIN, J.E., ADLINGTON, R.M., TURNER, N.J., DOMAYNE-HAYMAN, B.P., TING, H.H., DEROME, A.E., and MURPHY, J.A., *J. Chem. Soc., Chem. Commun.*, 1984, 1167.

23. BALDWIN, J.E., ADLINGTON, R.M., DEROME, A.E., TING, H.H. and TURNER, N.J., *J. Chem. Soc., Chem. Commun.*, 1984, 1211.

24. BAN, Y., WAKAMATSU, T., and MORI, M., *Heterocycles*, 1977, 6, 1711; OKITA, M., WAKAMATSU, T., and BAN, Y., *J. Chem. Soc., Chem. Commun.*, 1979, 749.

25. EASTON, C.J., and HAY, M.P., *J. Chem. Soc., Chem. Commun.*, 1985, 425.

26. KNUNYANTS, I.L., and GAMBARYAN, N.P., *Izv. Akad. Nauk. S.S.S.R. Otdel. Khin. Nauk.*, 1955, 1307.

27. HOLLEY, R.W., and HOLLEY, A.D., *J. Am. Chem. Soc.*, 1949, 71, 2124.

28. WASSERMAN, H.H., HLASTA, D.J., TREMPER, A.W., and WU, T.S., *Tetrahedron Lett.*, 1979, 20, 549.

29. TAKAHATA, H., OHNISHI, Y., TAKEHARA, H., TSURITANI, K., and YAMAZAKI, T., *Chem. Pharm. Bull.*, 1981, 29, 1063.

30. Sample supplied by Dr C.J. Easton.

31. BROWN, H.C., and ASH, A.B., *J. Am. Chem. Soc.*, 1955, 77, 4019; RUSSELL, G.A., and BROWN, H.C., *J. Am. Chem. Soc.*, 1955, 77, 4031.

32. PHILLIPOU, G., and BECKWITH, A.L.J., *Aust. J. Chem.*, 1976, 29, 1277; RAWLINSON, D.J., and SOSNOVSKY, G., *Synthesis*, 1972, 1.

33. BARROW, K.D., and SPOTSWOOD, T.M., *Tetrahedron. Lett.*, 1965, 6, 3325.

34. GASSMAN, P.G., and FOX, B.L., *J. Org. Chem.*, 1966, 31, 982.

35. WIJNBERG, J.B.P.A., SPECKAMP, W.N., and deBOER, J.J.J., *Tetrahedron. Lett.*, 1974, 46, 4073.

36. LIGHTNER, D.A., and PAK, C.S., *J. Org. Chem.*, 1975, 40, 2724.

37. APPLEWHITE, T.H., WAITE, H., and NIEMANN, C., *J. Am. Chem. Soc.*, 1958, 80, 1465.

38. SKELL, P.S., and TRAYNHAM, J.G., *Acc. Chem. Res.*, 1984, 17, 160.

39. EASTON, C.J., and HAY, M.P., Unpublished results.

40. KUIVILA, H.G., *Acc. Chem. Res.*, 1968, 1, 299.

41. KHARASCH, M.S., and BROWN, H.C., *J. Am. Chem. Soc.*, 1940, 62, 925.

42. JOHNSON, R.A., and GREENE, F.D., *J. Org. Chem.*, 1975, 40, 2186.

43. TESTA, E., FONTANELLA, L., CHRISTIANI, G., and GALLO,G., *J. Org. Chem.*, 1957, 24, 1928.

44. GREENE, J.L. and HAGEMEYER, H.J., *J. Am. Chem. Soc.*, 1955, 77, 3016.

45. VERKOYEN, C., and RADEMACHER, P., *Chem. Berichte.*, 1984, 117, 3048.

46. WASSERMAN, H.H., and LIPSHUTZ, B.H., *Tetrahedron. Lett.*, 1976, 17, 4613.

47. POHLOUDEK, F.R. and SCHROEPL, E., *Pharmazie*, 1968, 23, 561; *Chem. Abstract* 70:47346c.

48. MANHAS, M.S., and JENG, S.J., *J. Org. Chem.*, 1967, 32, 1246.

49. IKEDA, K., TERAO, Y., and SEKIYA, M., *Chem. Pharm. Bull.*, 1981, 29, 1747.

50. OVERMAN, L.E., and OSAWA, T., *J. Am. Chem. Soc.*, 1985, 107, 1698.

51. OKAWARA, T., MATSUDA, T., and FURUKAWA, M., *Chem. Pharm. Bull.*, 1982, 30, 1225.

52. HATADA, K., and ONO, Y., *Bull. Chem. Soc. Jpn.*, 1977, 50, 2517.

53. EASTON, C.J., and FINDLAY, N.G., *J. Labelled Compounds Radiopharmaceuticals*, 1985, 22, 667.

54. MATSUMOTO, T., *J. Fac. Sci. Hokkaido University*, Ser III, 1957, 5, 17; *Chem. Abstracts*, 12846h, 1958; EASTON, C.J., and BOWMAN, N.J., Unpublished results.

55. WASSERMAN, H.H., LIPSHUTZ, B.H., TREMPER, A.W., and WU, T.S., *J. Org. Chem.* 1981, 46, 2993.

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paper to accompany thesis by S.G. Love "Approaches to the Biomimetic Synthesis of β-Lactam Antibiotics"

DIRECT INTRODUCTION OF A BENZOYLOXY SUBSTITUENT AT THE C-4 POSITION OF β-LACTAMS

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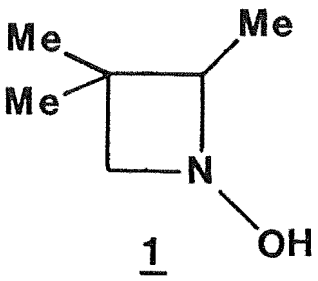
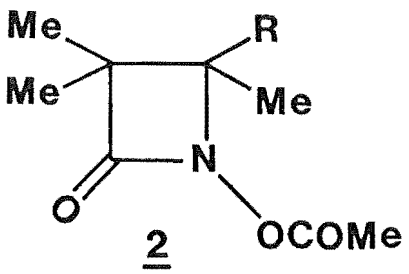
SUMMARY: The copper-promoted reaction of β-lactams with *t*-butyl perbenzoate results in benzoyloxylation of the azetidin-2-one ring at the C-4 position. There is no competing reaction at the C-3 position, but reaction at exocyclic carbon α to nitrogen competes with ring substitution.

One limit to the use of azetidinones in syntheses of β-lactam antibiotics[1] is a lack of methods for introducing a substituent directly at the C-4 position of an azetidinone ring. Oxidation of the hydroxyazetidine (1) with lead tetraacetate gave the 4-acetoxyazetidinone (2a), but this reaction is thought to occur by 1,3-addition of the oxidizing agent to the nitrone (3), not by direct substitution of the β-lactam (2b).[2] It has been



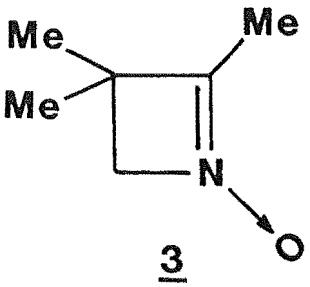
1



2

a, R=OCOMe

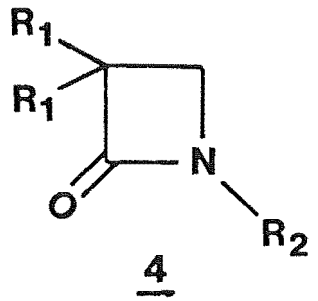
b, R=H



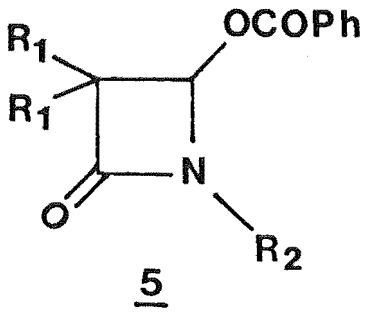
3

established that further substitution occurs at the azetidinone C-4 position when the site is already activated by adjacent sulphur.[3] In this communication we describe a method for functionalization of β-lactams at C-4 through the introduction of a benzoyloxy substituent. Our work is based on the knowledge that free-radical oxidation of γ- and δ-lactams occurs readily at the ring carbon α to nitrogen.[4]

The β-lactams (4a-g)[5] were prepared from corresponding 3-halopropionamides by treatment with sodium hydride.[6] To limit competing acrylamide formation in the preparations of 4a and 4b, the propionamides were added slowly, in dilute solution, to a thin suspension of sodium hydride.[7] The corresponding 3-iodopropionamide was used to prepare 4a.



4



5

a, $R_1 = H$, $R_2 = t\underline{Bu}$

b, $R_1 = H$, $R_2 = Ph$

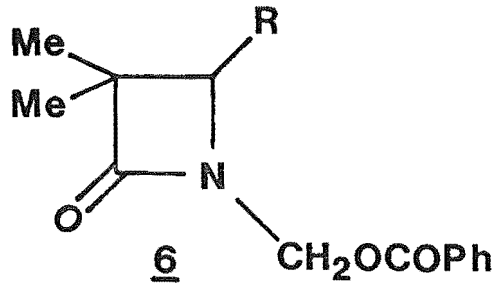
c, $R_1 = R_2 = Me$

d, $R_1 = Me$, $R_2 = CH_2Ph$

e, $R_1 = Me$, $R_2 = t\underline{Bu}$

f, $R_1 = Me$, $R_2 = Ph$

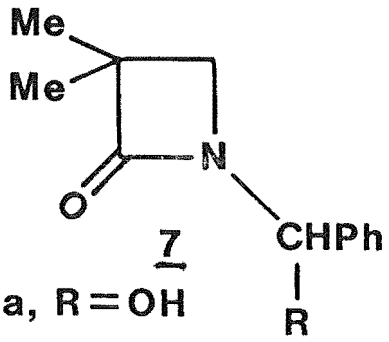
g, $R_1 = Ph$, $R_2 = t\underline{Bu}$



6

a, R = H

b, R = OCOPh



7

a, R = OH

b, R = OCOPh

Reaction of 4a (100mg, 0.8 mmol) with *t*-butyl perbenzoate (2.4 mmol) in the presence of cupric octanoate (0.02 mmol) in benzene (5ml) under nitrogen at reflux for 6 hr afforded, after chromatography on a Chromatotron silica gel plate, the 4-benzoyloxy substituted β-lactam (5a) [59%,[8] ^{1}H n.m.r. ($CDCl_3$) δ 1.40 (9H, s, *t*Bu), 2.81 (1H, dd, J 1,14Hz, C3-H*cis*), 3.33 (1H, dd, J 4,14Hz, C3-H*trans*), 6.34 (1H, dd, J 1,4Hz, C4-H), and 7.2-8.3 (5H, m, Ar-H)]. Similar treatment of 4b gave 5b [53%, ^{1}H n.m.r. ($CDCl_3$), δ 3.17 (1H, dd, J 2,16Hz, C3-H*cis*), 3.66 (1H, dd, J 4,16Hz, C3-H *trans*), 6.74 (1H, dd, J 2,4Hz, C4-H), and 7.1-8.3 (10H, m, Ar-H)]. The ^{1}H n.m.r. spectra of 5a and 5b show unambiguously that the benzoyloxy substituent has been incorporated at the C-4 position.[9] The geminal coupling constants indicate that the methylene group is adjacent to the amide carbonyl group.

The major features of the mechanism of reactions involving *t*-butyl perbenzoate have been elucidated.[10] Formation of 5a and 5b can be attributed to hydrogen-atom transfer from the corresponding β-lactams (4a) and (4b) to *t*-butoxy radical, followed by benzoate incorporation at the site of hydrogen abstraction. Clearly the C-4 methylene is more reactive than the C-3 position, presumably because of the activating effect of adjacent nitrogen.[4]

In order to examine the relative reactivity of an exocyclic carbon α to nitrogen as compared to an endocyclic carbon, the reaction of the β-lactam (4c) was investigated. The primary products of reaction of 4c with *t*-butyl perbenzoate were the endocyclic substitution product (5c) [^{1}H n.m.r. ($CDCl_3$), δ 1.33 (3H, s, CMe*cis*), 1.40 (3H, s, CMe*trans*), 2.91 (3H, s, NMe), 5.88 (1H, s, CH), and 7.3-8.3 (5H, m, Ar-H)] and the exocyclic substitution product (6a) [^{1}H n.m.r. ($CDCl_3$), δ 1.33 (6H, s, 2xCMe), 3.32 (2H, s, C-CH_2-N), 5.45 (2H, s, O-CH_2-N), and 7.3-8.3 (5H, m, Ar-H)] in the ratio *ca*.1:2. As the extent of reaction increased the disubstitution product (6b) [^{1}H n.m.r. ($CDCl_3$), δ 1.33 (3H, s, CMe*cis*), 1.45 (3H, s, CMe*trans*), 5.58 (2H, s,CH_2), 6.13 (1H, s, CH), and 7.3-8.3 (10H, m, Ar-H)] was also formed. Analysis of product ratios at varying extents of reaction showed that 6b is a secondary product formed by subsequent reaction of 5c and 6a. Formation of 5c, 6a, and 6b in the reaction of 4c demonstrates that reaction at exocyclic carbon α to nitrogen competes with ring substitution.

In the β-lactam (4f) the exocyclic carbon α to nitrogen is activated further by a phenyl substituent. The final product of reaction of 4f with *t*-butyl perbenzoate, isolated after chromatography, was the alcohol (7a) [12%, ^{1}H n.m.r. ($CDCl_3$), δ 1.26 (3H, s, Me), δ 1.33 (3H, s, Me), 2.68 (1H, d, *J* 6Hz, CH), 3.14 (1H, d, *J* 6Hz, CH), 4.30 (1H, b.s, OH), 6.36 (1H, s, CH), and 7.2-7.6 (5H, m, Ar-H)]. We attribute formation of this product to hydrolysis of the benzoate (7b) during chromatography. No ring substitution product was detected.

Finally we examined reactions of the β-lactams (4e-g) having substituents at C-3. Reactions of 4e and 4f afforded 5e [28%, ^{1}H n.m.r. (CCl_4), δ 1.10 (3H, s, Me*cis*), 1.34 (3H, s, Me*trans*), 1.39 (9H, s, *t*Bu), 5.88 (1H, s, CH), and 7.3-8.2 (5H, m, Ar-H)] and 5f [19%, ^{1}H n.m.r. ($CDCl_3$), δ 1.34 (3H, s, Me*cis*), 1.53 (3H, s, Me*trans*), 6.42 (1H, s, CH), and 7.1-8.3 (10H, m, Ar-H)], respectively. Relative yields of the benzoates (5a) and (5b) compared to (5e) and (5f) from reactions having the same molar ratio of perester indicate that substituents at C-3 reduce the reactivity. This steric effect accounts for the observation that the β-lactam (4g) was completely unreactive.

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REFERENCES AND NOTES

1. See for example K. Fujimoto, Y. Iwano and K. Hirai, Tetrahedron Lett., 1985, 26, 89; W.F. Huffman, K.G. Holden, T.F. Buckley, J.G. Gleason and L. Wu, J. Am. Chem. Soc., 1977, 99, 2352; T.N. Salzmann, R.W. Ratcliffe, B.G. Christensen and F.A. Bouffard, J. Am. Chem. Soc., 1980, 102, 6161; M.M. Campbell and B.P. Connarty, Heterocycles, 1982, 19, 1853; M.D. Bachi and A. Gross, J. Chem. Soc. Perkin Trans. I, 1983, 1157; M. Ihara, A. Nakayama and K. Fukumoto, Tetrahedron, 1982, 38, 2489.

2. M.L.M. Pennings and D.N. Reinhoudt, J. Org. Chem., 1983, 48, 4043.

3. H. Matsumura, T. Yano, M. Ueyama, K. Tori and W. Nagata, J. Chem.Soc. Chem. Commun., 1979, 485.

4. M. Okita, T. Wakamatsu and Y. Ban, J. Chem. Soc. Chem .Commun., 1979 749; M. Okita, T. Wakamatsu, M. Mori and Y. Ban, Heterocycles, 1980, 14, 1089; J.W. Pavlik and S. Tantayanon, J. Am. Chem. Soc., 1981, 103, 6755; J.C. Gramain, R. Remuson and Y. Troin, J. Chem. Soc. Chem. Commun., 1976, 194; for a review see T. Shono, Tetrahedron, 1984, 40, 811.

5. All new compounds were fully characterised.

6. I.L. Knunyants and N.P. Gambaryan, Izv. Akad. Nauk. SSSR, Otdel. Khim. Nauk, 1955, 1037.

7. H.H. Wasserman, D.J. Hlasta, A.W. Tremper and J.S. Wu, Tetrahedron Lett., 1979, 549.

8. Yields based on recovered starting material were virtually quantitative. Quoted yields are based on reaction with 3 molar equivalents of perbenzoate. Higher yields were obtained using larger excesses of perester.

9. K.D. Barrow and T.M. Spotswood, Tetrahedron Lett., 1965, 3325.

10. D.J. Rawlinson and G. Sosnovsky, Synthesis, 1972, 1.